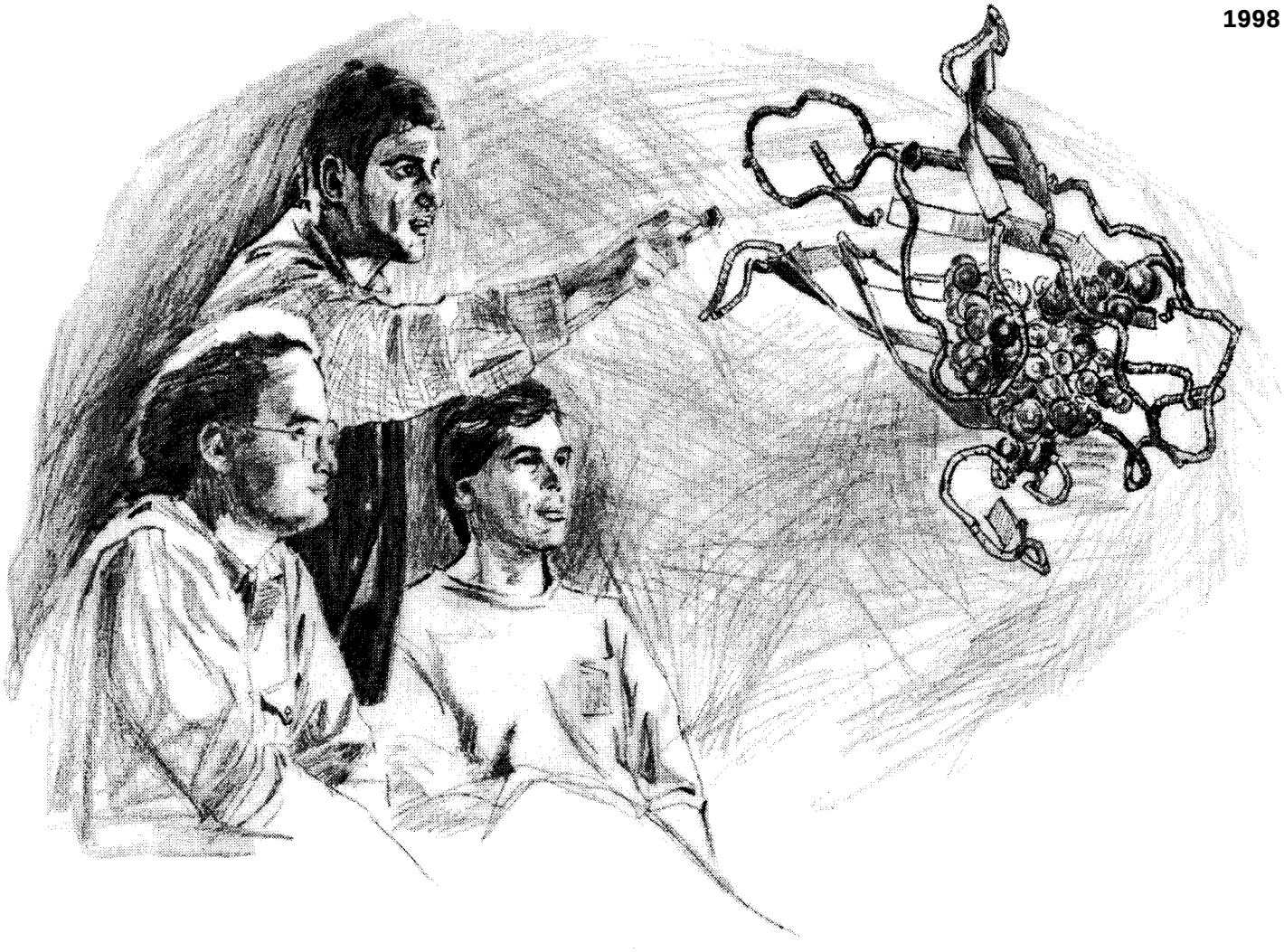
Biomedical Technology Resources

National Center for Research Resources

National Institutes of Health

A Research Resources Directory

1998



Contents

Mass Spectrometry

Optical and Electron Microscopy

Simulation and Computation

Synchrotron Radiation

Other Biomedical Technology Activities

Indexes

The Biomedical Technology area of the National Center for Research Resources (NCRR) has published this directory to promote access to a national network of biomedical technology resource centers.

NCRR funds biomedical technology resource centers at institutions across the country that are dedicated to technological research and development to help investigators solve research problems involving technological challenges. These centers provide state-of-the-art technologies and methods — generally unavailable through other sources — to thousands of biomedical investigators. Experts at the resource centers collaborate with biomedical researchers to create, develop, and provide a wide range of complex technological capabilities. The centers also offer research service and training in the use of new technologies. Internal advisory committees assist with evaluating applications for user access.

In this directory, the centers are organized into the following categories: bioengineering, flow cytometry, integrated technologies, isotopes and particles, laser applications, magnetic resonance imaging (structure and function), magnetic resonance spectroscopy, mass spectrometry, optical and electron microscopy, simulation and computation, and synchrotron radiation. Each entry includes the principal investigator and contact person, the research being conducted, and the capabilities of the resource that are available to outside investigators.

NCRR encourages qualified biomedical scientists to take advantage of the unique capabilities of the centers listed in this directory, and welcomes comments on their usefulness and the need for additional technologies.

Descriptions of biomedical technology grant mechanisms are also included. These mechanisms include biomedical technology resource grants, investigator-initiated biomedical technology research grants, exploratory/developmental grants, shared instrumentation grants, and small business grants.

For more information about NCRR Biomedical Technology programs, please visit our Web site at http://www.ncrr.nih.gov or contact:

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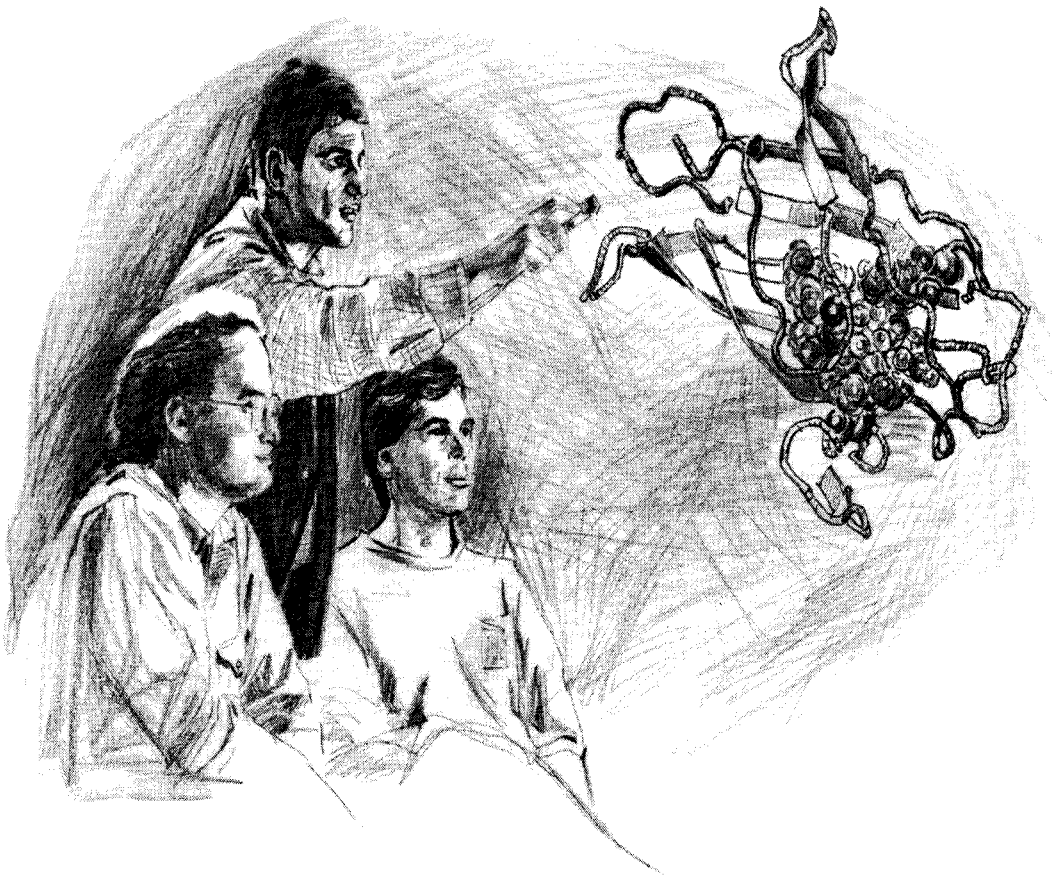
Directory Organization

The directory of biomedical technology resource centers is organized into broad technological categories as indicated in the Contents. Within each category, resources are listed alphabetically by title. Descriptions of biomedical technology grant mechanisms follow.

At the end of the directory, the name index lists principal investigators and contact persons alphabetically with their affiliations; the geographic index lists resources alphabetically by state and then by title.

Bioengineering



Biocalorimetry Center

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Research Emphasis

The focus of this resource is on thermodynamics and calorimetry applied to biomedical research. In particular, new strategies for protein and drug design are being developed using a structure-based thermodynamic approach. The state-of-the-art calorimetric instrumentation available at the center permits exploration of the energetics of ligand binding, protein folding, macromolecular associations, conformational equilibrium, and enzymatic reactions.

Current Research

The central problem in the design of proteins or ligands is the prediction of the structural stability or the binding affinity from structural considerations. This goal requires precise mathematical functions that relate the Gibbs energy or its components (enthalpy, entropy, heat capacity) to structure at the atomic level. The strategy devised at the Biocalorimetry Center has resulted in the development of a structural parameterization of the energetics based on precise calorimetric measurements of energetics parameters for proteins, peptides, and ligands. This approach has been shown to accurately predict the stability of proteins and the binding affinity of ligands from high-resolution structures. Four areas of research are currently considered: parameterization of folding and binding energetics; protein stability; binding and molecular recognition; and structure-based design.

A complete characterization of the folding or binding energetics also requires identification of the relative contributions provided by each residue or atom to the overall energetics. The resulting structural dissection of the energetics is used in the development of molecular design strategies. The approach used in this laboratory involves the use of the structural parameterization of the energetics in conjunction with the high-resolution structures of the molecules under consideration. The validity of the structure-based calculations is tested by measuring key thermodynamic quantities. This approach has been applied to different aspartic proteases including the HIV-1 protease.

Resource Capabilities

Instruments

High-sensitivity differential scanning calorimeters with the capability of absolute heat capacity measurements. High-sensitivity isothermal titration and flow-mix reaction calorimeters.

Continuous titration calorimeter. Silicon Graphics workstations for structure-based thermodynamic analysis of protein folding and binding.

Software

Algorithms developed in this laboratory have been implemented as in-house computer programs. They include software for analysis and modeling of calorimetric data, and software for structure-based thermodynamic analysis and molecular design.

1. Bardi, J. S., Luque, I., and Freire, E., Structure-based thermodynamic analysis of HIV-1 protease inhibitors, *Biochemistry* 36:6588–6596, 1997.
2. Luque, I., Mayorga, O. L., and Freire, E., Structure-based thermodynamic scale of alpha-helix propensities. *Biochemistry* 35:13681–13688, 1996.
3. Hilser, V. and Freire, E., Structure-based calculation of the equilibrium folding pathway of proteins: Correlation with hydrogen exchange protection factors. *Journal of Molecular Biology* 262:756–772, 1996.
4. D'Aquino, J. A., Gomez, J., Hilser, V. J., Lee, K. H., Amzel, L. M., and Freire, E., The magnitude of the backbone conformational entropy change in protein folding. *Proteins* 25:143–156, 1996.

BioCurrents Research Center

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Research Emphasis

The Center researches and develops techniques for the noninvasive measurement of biologically important molecular flux across cell membranes. All instruments rely on the unifying principle of drift and noise reduction by creating self-referencing systems. Four techniques are available: The self-referencing voltage (Serv), ion-selective (Seris), polarographic (Serp), and BioKelvin probes. Ion-selective systems can measure relatively steady-state calcium, potassium, and proton fluxes. The polarographic system, designed and successfully developed for measuring single cell oxygen consumption, is being diversified to measure nitric oxide and ascorbic acid flux. The BioKelvin probe operates in an aerial environment measuring voltage fields generated by subsurface ionic currents or surface charges.

Current Research

Current research and development includes further improvement of the original Serv and Seris systems. Particular goals for the Seris and Serp systems are to expand the number of detectable molecules and to continue integrating these technologies with conventional electrophysiological approaches. A new approach to remote electrode position will depend on robotic vision with near-real–time responsiveness and submicron resolution. The BioKelvin probe, currently operating as a four-head scanning device, is being modified to operate as a differential scanner for planar surfaces. Biological studies are diverse, ranging from work on single cells, through tissues, to whole organisms. Studies focus on the role of molecular transport in cell physiology and development, with emphasis on characterizing transport mechanisms. To facilitate this the Center is constructing a database of pharmacological products that will be appended to our Web site.

Resource Capabilities

Instruments

The resource offers a diverse range of instrumentation, servicing both in-house R&D and visiting investigators. Resource staff design and manufacture amplifiers, microstepper motion controllers and manipulators. There are six experimental platforms, five equipped with compound microscopes, four inverted (three Zeiss IM 35s and one Zeiss Axiovert) and one upright (Zeiss AxioScope). The Axiovert also has an Attofluor Ratio imaging system installed. Two platforms are temperature controlled either through stage temperature regulation or by an enclosing chamber. All Seris and Serp systems can collect differential and direct current values from two different modalities simultaneously.

Also, conventional electrophysiological techniques are supported, as is microinjection. Culture facilities are available for both mammalian and nonmammalian systems. A comprehensive list of equipment available at the BRC is available through our Web page with links to the extensive facilities available at the Marine Biological Laboratory, our host institution.

Software

All experimental platforms run on Pentiums. The data collection and motion-controlling program (IonView) runs through Windows 95. All Center computers are linked to an internal network and to the WWW via the MBL Unix.

1. Land, S.C., Sanger, R. H., and Smith, P. J. S., O_2 availability modulates transmembrane Ca^{2+}-flux via second messenger pathways in anoxia-tolerant hepatocytes. *Journal of Applied Physiology* 82:776–783, 1997.
2. Knox, R. J., Kao, L. S., Jonas, E., Smith, P. J. S., Connor, J. A., and Kaczmarek, L. K., Ca^{2+} influx and activation of a cation current are coupled to an intracellular Ca^{2+} mobilization of peptidergic neurons. *Journal of Physiology* 494:627–639, 1996.

Biomedical Simulations Resource

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Research Emphasis

The Biomedical Simulations Resource (BMSR) develops mathematical models and simulations of physiological systems as well as novel modeling methodologies for the experimental study of a number of biological processes. Emphasis is on nonlinear and nonstationary time-series models, with applications to sensory, neuronal, and biomechanical systems; sparse-data system modeling, with applications to pharmacokinetics and pharmacodynamics; and modeling of biological control systems, with applications to cardiorespiratory control.

Current Research

Development of modeling methodologies for nonlinear and nonstationary dynamic systems, sparse-data systems, and biological control systems. Application areas include sensory and neuronal systems, Drs. Vasilis Z. Marmarelis and Theodore W. Berger; pharmacokinetics and pharmacodynamics, Dr. David Z. D'Argenio; and cardiorespiratory control, Dr. Michael C. K. Khoo. Modeling and simulation software for these novel methodologies is developed and disseminated for use by the biomedical community at large.

Resource Capabilities

Instruments

A local area network of seven Sun workstations, including SPARCstation 20s, ultra 1s and ultra 2s serves the computational needs of BMSR investigators. A Sun SPARCstation 20 (128 MB Ram, 9 GB disk) provides both computer and disk server functions. The network also includes eight Pentium class PCs. The BMSR network is part of the University of Southern California's high-speed, multiprotocol network that connects hundreds of computers on both the University Park and Health Sciences campuses through optical fiber as well as thick- and thin-wire Ethernet.

Software

The BMSR develops, distributes, and supports two specialized software packages incorporating the resource's novel methodologies. LYSIS (Greek for "solution") is an interactive modular software package of programs performing high-level tasks that can be used for linear and nonlinear time-series analysis, and system modeling and simulation developed under the supervision of Dr. Marmarelis. ADAPT II is a set of high-level programs for simulation, data analysis and design of experiments, designed primarily for basic and clinical research modeling and data analysis applications involving pharmacokinetic and pharmacodynamic systems developed under the supervision of Dr. D'Argenio.

1. Marmarelis, V. Z., Modeling methodology for nonlinear physiological systems. *Annals of Biomedical Engineering* 25:239–251, 1997.
2. Khoo, M. C. K., ed., *Bioengineering Approaches to Pulmonary Physiology and Medicine*. New York: Plenum, 1996.
3. Liaw, J. S. and Berger, T. W., The dynamic synapse: A new concept for neural representation and computation. *Hippocampus* 6:591–600, 1996.
4. D'Argenio, D. Z., ed., *Advanced Methods of Pharmacokinetics and Pharmacodynamic Systems Analysis*, vol. 2. New York: Plenum, 1995.

Computer Vision Center for Vertebrate Brain Mapping

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Research Emphasis

Algorithms for use in neuroscience research. Types of data extractable with software designed here: High-precision maps of neurotransmitter receptors, distribution maps of specific mRNA, determination of metabolic rates for brain subregions, identification of sites of binding of pharmaceuticals. Data derived using different histological procedures can also be combined using the center's software.

Current Research

A research program in biological, mathematical, statistical, and computer vision methods for neurocartography. Techniques to construct and to employ 3-D probability brain atlases. These atlases have prototypical anatomy and data on interanimal variability. High-resolution atlases of this type for the rat are available and define the coordinate space for this species. Algorithms to automate mapping experimental histological data into those coordinates are being developed. Once in atlas space, the data from different animals using different histological procedures can be combined into a single multidimensional representation.

Resource Capabilities

Facility

The resource includes both computer and biology laboratories. Numerous workstations and desktop computers accommodate processing and visualization of large 3-D data sets. Image acquisition facilities include high-resolution scanners for histological material. The biology laboratory includes a large-tissue Cryopolycut cryostat that features low-distortion cryosection tape-support system and high-resolution blockface imaging. Also available in the histology lab is a custom-built high-resolution 3-D structured-light scanner for surface mapping of the brain surface prior to cryosectioning. This surface map can be employed for automatic 3-D reconstruction of tissue. Computer facilities consist of image analysis and visualization packages on workstations and personal computers.

Service Personnel and Services

Two software applications are available. BRAIN, a Mac application used in imaging and analysis of autoradiograms, supports both densitometric and grain counting. ALIGN is a UNIX and Mac application for registering sections, sections to volume, and volumes.

User Laboratory Space

Two image-processing workstations are available for use by the research community. These include high-resolution histological section scanners and a Zeiss Axoplan microscope. Histological facilities for atlas construction are also available.

1. Cohen, F. S., Yang, Z., Nissanov, J., and Huang, Z., Automatic matching of homologous histological sections. *IEEE Transactions in Biomedical Engineering*, in press.
2. Morano, R. A., Ozturk, C., Conn, R., Dubin, S., Zietz, S., and Nissanov, J., Structured light using pseudo-random codes, *IEEE Transactions on Pattern Analysis and Machine Intelligence*, in press.
3. Kozinska, D., Tretiak, O. J., Nissanov, J., and Ozturk, C., Multidimensional alignment using the Euclidean distance transform. *Computer Vision/Graphics Image Processing* 59:373–387, 1997.
4. McEachron, D. L., Nissanov, J., and Tretiak, O., Region-specific tritium enrichment, and not differential b-absorption, is the major cause of quenching in film autoradiography, *Physics and Biological Medicine* 42:1121–1132, 1997.
5. Chaudhuri, A., Nissanov, J., Larocque, S., and Rioux, L., Dual activity maps in primate visual cortex produced by different temporal patterns of zif268 mRNA and protein expression. *Proceedings of the National Academy of Sciences USA* 94:2671–2675, 1997.

Michigan Center for Neural Communication Technology

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Research Emphasis

Develop multichannel thin-film devices on silicon substrates to investigate complex neural systems; observe and influence the activity of cells and deduce neural circuits and geometric relationships; develop devices that function as multichannel sensors or permit multichannel microliter injection of chemical agents, or both at the same time.

Current Research

Three projects extend base technology, provide methods to analyze recorded signals from implanted devices, and develop histological means by which tissue-containing devices can be evaluated.

Project I extends micromachined electrode-recording technologies beyond recording and stimulation, to make electrodes more versatile by giving them additional ways to interact with surrounding cells. The initial project is a probe that releases chemical agents into the neural environment that can be used to change the neural function during an experiment by the use of chemical modulators.

Project II addresses biological neural networks (NNs) in the auditory system in the context of high-channel count electrodes. The enhanced data gathering made possible by thin-film, multicontact electrode technologies and the signal processing of data from close-packed arrays are applied to advance network estimation for NNs and to understand neural processing in auditory system networks by detection and analysis of neural discharges and their stimulus-related spike trains. Collection and analysis of multiple spike train data from the cochlear nucleus, the inferior colliculus, and the auditory cortex using sound stimuli are ongoing; local chemical and electrical stimuli in guinea pigs is beginning.

Project III assesses the probe in its tissue environment to identify and characterize cellular elements in the tissue that interact with the probe. Objectives: To further characterize the cells the probe is recording from by combining physical information with geometric information to identify the actual cells involved in chronic recordings; to generate quantitative information on cellular elements. A key technology allows the probes to be sectioned in place with the tissue and viewed with the confocal microscope.

Resource Capabilities

Center staff consult with users by telephone, fax, and e-mail and coordinate communication among them (cnct@umich.edu). Commercial companies can provide coatings and bonding to the probes, thereby increasing their utility. Short user visits are welcome; new users are shown implantation techniques and data acquisition methods, sometimes with the user's own preparation. Devices and services are discussed with potential users at the annual Neuroscience Society meeting. Standard probe designs are fabricated to maintain a stock for distribution to users and some devices custom-designed for advanced users for specific experiments. Because all devices are designed with a single set of design rules, many different devices are produced in a given fabrication run.

1. Chen, J. K., Wise, K. D., Hetke, J. F., and Bledsoe, S. C., A multichannel neural probe for selective chemical delivery at the cellular level. *IEEE Transactions in Biomedical Engineering* 44:760–769, 1997.
2. Kandel, A. and Buzsaki, G., Cellular-synaptic generation of sleep spindles, spike-and-wave discharges, and evoked thalamocortical responses in neocortex of the rat. *Journal of Neuroscience* 17:6783–6797, 1997.
3. Finger, P. A., Anderson, D. J., Edwards, C. A., Wiler, J. A., Hetke, J. F., and Altschuler, R. A., Morphological evaluation of chronically embedded 3-D silicon substrate electrodes in cat neurocortex. *27th Annual Meeting of the Society for Neuroscience*, 1997.

National ESCA and Surface Analysis Center for Biomedical Problems

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Research Emphasis

The National ESCA and Surface Analysis Center for Biomedical Problems (NESAC/BIO) employs surface analysis methods to solve biomedical research problems. The surface structure and composition of a biological or synthetic material, which is usually different from the bulk structure and composition, mediates the biological reactions occurring with that material. NESAC/BIO combines the latest surface analysis instrumentation with specialized experimental protocols and data analysis methods to provide a detailed understanding of surface structure and composition. Surface analysis addresses a wide range of biomedical device and materials issues, including contamination detection, unknown identification, quality control, failure analysis, surface property correlations with biological performance, and basic research.

Current Research

Instrument development projects include cold stages for freeze-dried analysis of hydrated biological samples. Data analysis methods include development of algorithms for inversion of angle-dependent electron spectroscopy for chemical analysis (ESCA) data into compositional depth profiles and multivariate statistical analysis of secondary ion mass spectrometry (SIMS) data. A systematic study of standard materials (polymers, self-assembled monolayers, ordered protein films, etc.) is an ongoing project to improve ability to characterize the surface structure and composition of complex biological materials (proteins, cells, etc.).

Resource Capabilities

ESCA and SIMS systems are the primary surface analysis instrumentation available at NESAC/BIO. ESCA technique provides quantitative analysis (±5%) of all elements except H and He in the outer 100 Å of a sample, with details about the bonding environment and oxidation state of each element. Angle-dependent ESCA is available for nondestructive determination of the compositional variation from the surface down to 100 Å into the sample. Hydrated materials can be examined using in situ freeze-drying. The static SIMS technique provides mass spectra and images of the outermost 10–15 Å of a sample. Positive and negative secondary ions can be collected in both spectra and imaging modes and provide detailed molecular structural information about the surface. The high sensitivity (ppm to ppb) and high mass resolution ($m/\Delta m > 5000$) of static time of flight (ToF) SIMS can detect and identify trace components. Additional instrumentation available here includes scanning tunneling microscopy, atomic force microscopy, Fourier transform infrared spectroscopy, and contact angle measurement.

Instruments

Two monochromatized ESCA systems (Surface Science Instruments X-probe and S-probe) are each equipped for automated multisample, angle-dependent, and frozen-hydrated analysis of biological materials at spatial resolutions down to 150 µm. A reflectron ToF SIMS system (Physical Electronics 7200) is equipped with a Cs ion source for acquiring spectra and images of biological materials at spatial resolutions down to 5 µm. A quadrupole SIMS systems (Physical Electronics 3700) is equipped with liquid nitrogen-cooled sample stages for frozen-hydrated analysis of biological materials.

1. Ratner, B. D. and Castner, D. G., Electron spectroscopy for chemical analysis, in *Surface Analysis–Principal Techniques* (Vickerman, J. C., ed.). New York: John Wiley and Sons, 1997, pp. 43–98.
2. Bearinger, J. P., Castner, D. G., Golledge, S. L., Rezania, A., Hubchak, S., and Healy, K. E., p(AAm-*co*-EG) interpenetrating polymer networks grafted to oxide surfaces: Surface characterization, protein adsorption, and cell detachment studies. *Langmuir* 13:5175–5183, 1997.
3. Tidwell, C. D., Ertel, S. I., Ratner, B. D., Tarasevich, B., Atre, S., and Allara, D. L., Endothelial cell growth and protein adsorption on terminally functionalized, self-assembled monolayers of alkanethiolates on gold. *Langmuir* 13:3404–3413, 1997.

Resource on Medical Ultrasonic Transducer Technology

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Research Emphasis

The focus of this resource is on the development of very high frequency (20 to 80 MHz) ultrasonic transducers/arrays for applications in medicine and biology that include ophthalmology, dermatology, and vascular surgery. The research is pursued simultaneously in three directions: Novel piezoelectric materials, very high frequency linear arrays, and finite element modeling and material property measurements.

Current Research

Single crystal ferroelectric relaxor materials of varying composition (PZN-PT and PMN-PT) and fine-grain PZT are being prepared and tested for their suitability as very high frequency transducer materials. The feasibility of preparing high-performance piezocomposites from single crystal and PZT for very high frequency applications is being studied. A flexible multichannel beamformer capable of handling frequencies higher than 100 MHz and a high frame rate ultrasonic biomicroscope are being developed. Finite element modeling tools are being used to simulate beamforming of phased array, to examine the effect of acoustic cross-talk, and to investigate different transducer and piezocomposite design strategies. Elastic and acoustic properties of transducer materials–including lens, matching layer, backing block, and filler needed for modeling–are being measured.

Resource Capabilities

Hardware

K & S 782 dicing saw, Parylene coating system, DC magnetron sputtering system, lapping and grinding machines, lathe, multichannel 250 MHz digitizers, 125 MHz HP hydrophone, 40 MHz membrane hydrophone, Intec Optison real-time schlieren system, 100 MHz and 500 MHz HP electrical impedance analyzers, Ultraoptec OP35-I/O laser interferometer, LeCroy high-frequency digitizing scopes and Sun workstations.

Software

KLM transducer modeling packages, ANSYS frequency domain finite element analysis software, SPICE circuit analysis software, and PZFlex time domain finite element analysis software.

Service Personnel and Services

Two full-time engineers and one full-time technician are available for consultation and to assist in device design and fabrication. Resource facilities are available for transducer design and fabrication and training.

1. Park, S. E., and Shrout, M. R., Characteristics of relaxor-based piezoelectric single crystals for ultrasonic transducers. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control* 44:1140–1147, 1997.
2. Qi, W. and Cao, W., Finite element analysis of periodic and random 2-2 piezocomposite transducers with finite dimensions. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control* 44:1168–1171, 1997.
3. Zipparo, M. J., Shung, K. K., and Shrout, T. R., Piezoceramics for high frequency (20 to 100 MHz) single-element imaging transducers. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control* 44:1038–1048, 1997.
4. Schneider, B. and Shung, K. K., Quantitative analysis of pulsed ultrasonic beam patterns using a schlieren system. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control* 43:1181–1186, 1996.

Simulation Resource in Mass Transport and Exchange

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Research Emphasis

The focus of this resource center is to develop modeling and simulation software to estimate conductances of capillary and cell membranes, volumes of distributions, and regional flows. This effort includes identification of receptor affinities and metabolic rates in intact organs and image regions of interest via various tracer techniques.

The resource has developed a library of mathematical subroutines for modeling circulatory mass transport and exchange that are available to the research community. The resource has also developed interactive simulation interfaces that run under the Unix operating system. A command-driven interface (SIMCON) is available. The X-Window multitasking interface (XSIM) is now available for Sun (SunOS Releases 4 & 5) and SGI (IRIX Release 6) workstations.

Current Research

Continued development of the XSIM interface that is focused on the integration of advanced graphics techniques to display the behavior of models and the results of simulation analysis, expanded parameter optimization capabilities, and porting to additional platforms.

Application areas include transport of hydrophilic molecules in microvasculature, simulation analysis for estimation of tracer uptake and deposition in cells as indicators of regional blood flow and cellular function. Use of fractals to describe heterogeneous systems (e.g., spatial and temporal flow variations).

A rapidly enlarging program area is the Physiome Project, an international effort to bring together elements from genome, proteome, and molecular biology into cellular biology and integrative physiology. The particular emphasis at this resource center is on the CArdiome, the functioning heart.

Resource Capabilities

Hardware

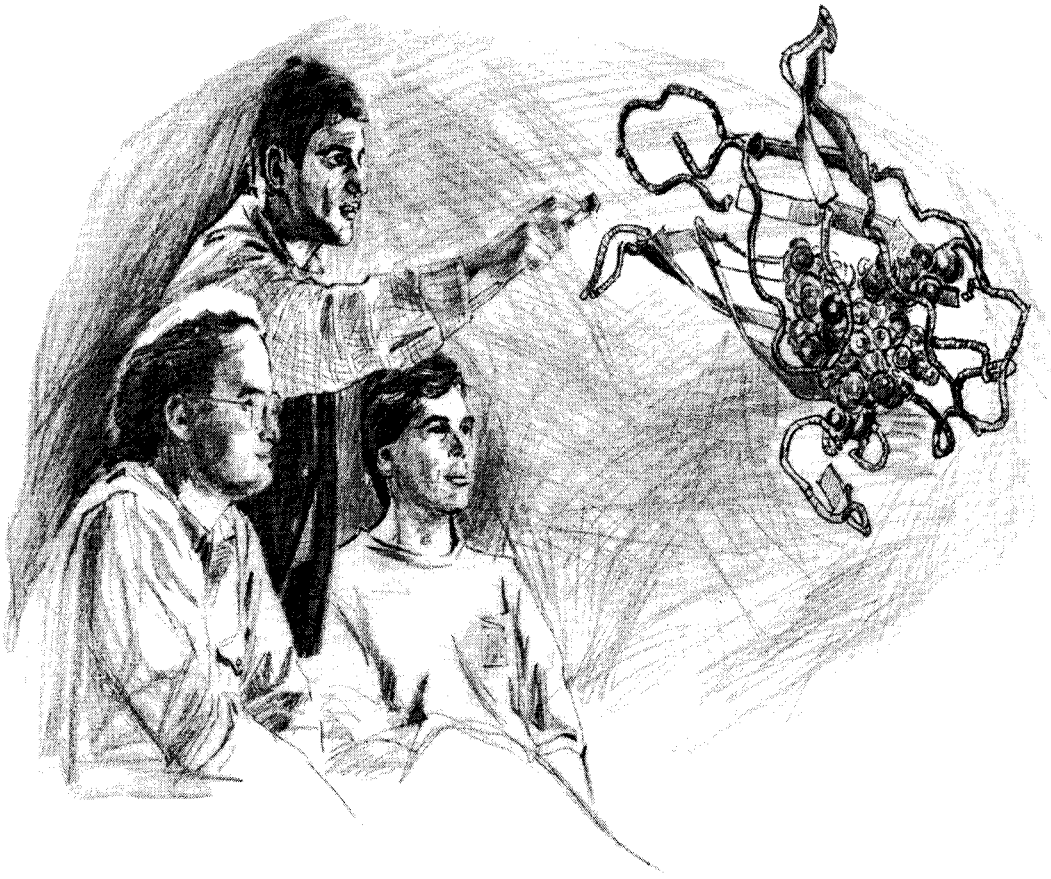
Network of 16 Sun SPARCstations, one SPARCserver, one SGI Indigo^2 workstation, one DEC Alpha, and two Pentium-based LINUX workstations with a total disk storage capacity in excess of 20 gigabites, 800/1600/6400 bpi tape drive, and cartridge tape drives; monochrome X terminals; modem connections to 14,400 baud; color laser printer; MS-DOS and Mac microcomputers.

Software

SUN Unix operating system; FORTRAN and C compilers; S+, Maple, Matlab programs; FrameMaker document processing program.

1. Li, Z., Yipintsoi, T., and Bassingthwaighte, J. B., Nonlinear model for capillary-tissue oxygen transport and metabolism. *Annals of Biomedical Engineering* 25:604–619, 1997.
2. Bassingthwaighte, J. B., A design and strategy for the cardiome project. In: *Analytical and Quantitative Cardiology*, edited by S. Sideman and R. Beyar. New York: Plenum, 1997, chap. 28, pp. 325-339.
3. Cannon, M. J., Percival, D. B., Caccia, D. C., Raymond, G. M., and Bassingthwaighte, J. B., Evaluating scaled windowed variance methods for estimating the Hurst coefficient of time series. *Physica* A 241:606–626, 1997.
4. Kroll, K. and Stepp, D. W., Adenosine kinetics in the canine coronary circulation. *American Journal of Physiology* 270 (*Heart Circulation Physiology* 39):H1469–H1483, 1996.

Flow Cytometry



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URL: http://www-ls.lanl.gov/NFCR/

Research Emphasis

The National Flow Cytometry Resource advances flow cytometric analyses through innovative research, development, and collaborations. Flow cytometry is a technique for high-speed analysis of biological particles ranging in size from single molecules and macromolecular complexes to subcellular organelles, cells, and cellular aggregates. Particles pass rapidly through one or more focused laser beams where probe molecules bound to specific components, such as DNA in cells, are excited and the emitted fluorescence photons are detected. Measurement of fluorescence emissions and scattered excitation light provide quantitative information about the particles. For cells, DNA, RNA, and protein content; surface molecules; and physiological parameters are measured. Since individual particles are analyzed, distributions of these and other measured parameters are obtained at analysis rates of thousands of events per second. Based on the measurements, particles in selected subpopulations can be physically separated by sorting. Unique flow cytometric capabilities include high-resolution chromosome analysis and sorting; multilaser excitation systems: Coulter volume-based sorting, fluorescence lifetime measurement; rapid-mix analyses with subsecond time resolution; phase-sensitive fluorescence detection; DNA fragment size quantification; ultrasensitive fluorescence detection; and multivariate data display and analysis. Expert advice and assistance are available to collaborators preparing cellular and chromosome samples for analysis; fluorescent staining of cellular components, rapid kinetic analyses, macromolecular assembly dynamics, multivariate data acquisition and analysis; sorting procedures; and other areas.

Current Research

Microsphere-based analysis of molecular interactions; kinetic analyses of signal transduction processes in cells; and DNA fragment size distribution analyses. Associated research: Cell cycle analysis and control; applications of chromosome analysis and sorting in neoplastic transformation; chromosome sorting for recombinant DNA library construction; analysis of wild-type and mutant endonuclease activities; bacterial identification; and medical applications of flow cytometry.

Resource Capabilities

Instruments

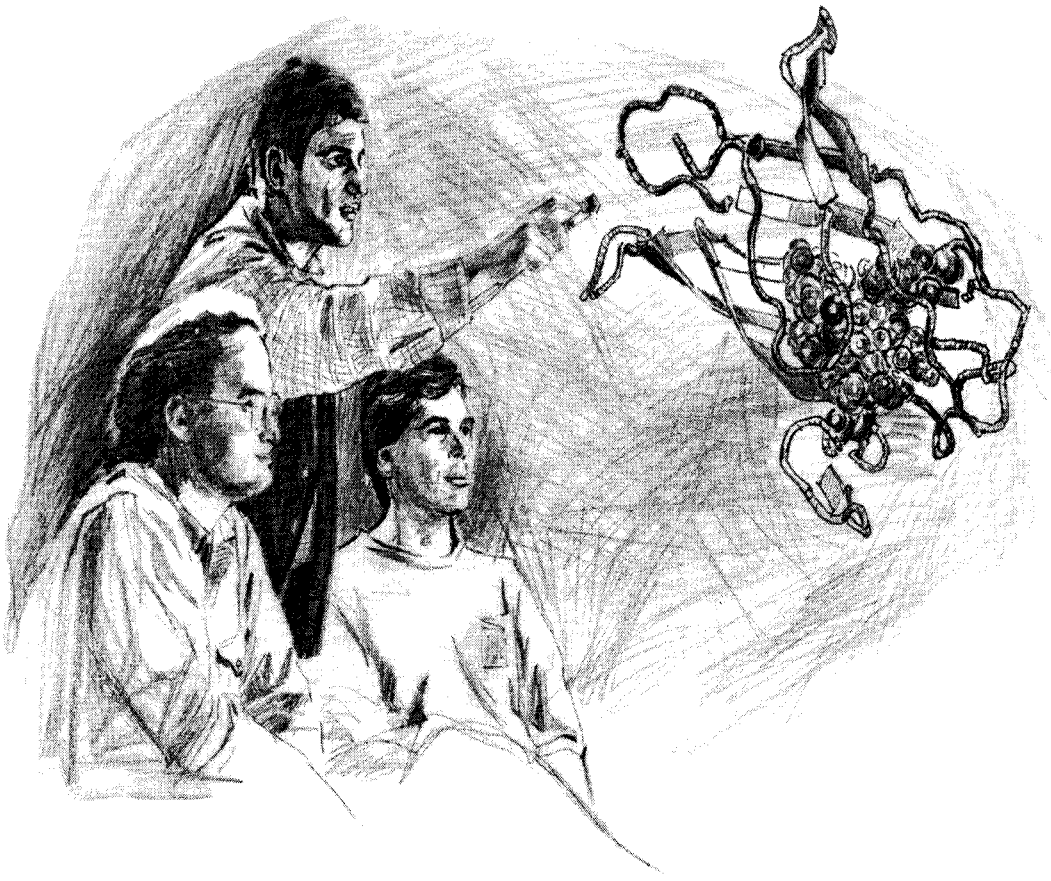
Four multiwavelength sorting systems with two or three lasers for sequential excitation (high- and low-power Argon, Krypton lasers), phase-sensitive/lifetime flow cytometer, rapid mix flow cytometer, DNA fragment-size analysis cytometer; optical chromosome selection cytometer; BD FACSCaliber five-parameter cytometer; fluorescence microscope with cooled CCD camera; and static and time-resolved spectrophotometers.

Special Features

Data acquisition capabilities for up to 512 parameters per event; axial light loss measurements; Coulter volume; multiwavelength excitation/emission measurements; rapid-mix/sample delivery with subsecond capabilities; bulk chromosome sorting; off-line data analysis with local workstations or central computing facility.

1. Wimmer, K., Thoraval, D., et al., Two-dimensional separation and cloning of chromosome 1 notI-EcoRV-derived genomic fragments. *Genomics* 38:124–132, 1996.
2. Nolan, J. P., Shen, B., Park, M. S., and Sklar, L. A., Kinetic analysis of human flap endonuclease-1 by flow cytometry. *Biochemistry* 35:11668–11676, 1996.
3. Sailer, B. L., Natasi, A. J., Valdez, J. G., Steinkamp, J. A., and Crissman, H. A., Interactions of intercalating fluorochromes with DNA analyzed by conventional and fluorescence lifetime flow cytometry utilizing deuterium oxide. *Cytometry* 25:164–172, 1996.
4. Huang, Z., Petty, J. T., et al., Large DNA fragment sizing by flow cytometry: Application to the characterization of P1 artificial chromosome (PAC) clones. *Nucleic Acids Research* 24:4202, 1996.

Integrated Technologies



Comprehensive Biology–Exploiting the Yeast Genome

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Research Emphasis

The complete genomic sequence of the yeast *Saccharomyces cerevisiae* has identified a little over 6000 genes, less than half of which have been assigned a function. The concept of this Center is to provide a central resource where a variety of technologies can be applied to identify the functions of yeast genes, and to uncover novel genes and proteins implicated in various biological processes. The Center works with consortia, small groups of scientists with research interests in a similar area and who are willing to share unpublished data that emerge from collaborations with us. The scientists within a consortium work at distant sites from each other, as well as from the University of Washington, and their collaboration is facilitated by an electronic networked collaboration management system.

The technologies employed by the Center are two-dimensional gel electrophoresis for high-resolution separation of proteins; mass spectrometry as part of a protein identification strategy that can analyze components in protein mixtures without prior separation and that can be used to study modifications of proteins; two-hybrid analysis of protein-protein interactions; computational approaches for protein and DNA analysis to identify patterns such as coregulated genes; and DNA arrays for hybridization to carry out a genomic analysis of transcript levels. An electronic networked "collaboratory" provides the information management and systems for online collaboration among Center scientists. A facet of this collaboratory is the Moulage data representation and analysis system, and an extensive Web site for the Center.

Current collaborations focus on these areas of yeast biology: Cellular response to DNA damage, the mating pheromone response pathway, development of cell polarity, and transcriptional control.

Resource Capabilities

Instruments

Finnigan MAT LCQ electrospray ion trap mass spectrometer, PerSeptive Biosystems Integral, HP1100 HPLC, LC Packing's FAMOS autosampler, Molecular Dynamics Microarray System Generation II.

Software

SEQUEST software for database searching using MS/MS spectra of peptides, Moulage data analysis and integration system, Oracle Interoffice collaboration management system, Consensus program for discovering patterns in common to a collection of sequences, Patser program for searching a sequence with a pattern (or matrix that represents that pattern), MatrixSearch program that takes a library of patterns (represented as matrices) and searches for all occurrences in a sequence.

Resource Center for Biomedical Complex Carbohydrates

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Research Emphasis

Initial characterization of complex carbohydrates including estimation of sample purity, glycosyl composition analysis, glycosyl linkage analysis, 1-D NMR analysis, and molecular weight determinations using gas-liquid chromatography-mass spectrometry; electrospray ionization, fast-atom-bombardment, matrix-assisted laser desorption/ionization time-of-flight, and tandem mass spectrometry; and 300-, 500-, 600-, and 800-MHz ^{1}H- and ^{13}C-NMR spectroscopy. More sophisticated, customized, or nonroutine services can be individually designed and/or set up as a more extensive, collaborative investigation. A program for computer-assisted pattern recognition analysis of the structures of complex carbohydrates using artificial neural networks is available at the center's Web site.

Current Research

Complete structural characterization of a complex carbohydrate involves determining the primary structure as well as the 3-D structure. For glycoproteins, this also involves identification of the position in the protein to which the carbohydrate is attached. Computer-assisted methods for structural characterization of oligosaccharides; pattern recognition techniques based on artificial neural networks. MS techniques for analysis of oligosaccharides; linkage and stereochemical analysis of glycosyl residues of oligosaccharides using MS; determination of glycosylation sites, carbohydrate side chain identification, and side chain heterogeneity of glycoproteins and/or glycopeptides by HPLC/MS and HPLC/MS/MS. C-type lectins in *Xenopus laevis*: Structure, expression, and analysis of glycoconjugate ligands; roles of carbohydrate-protein/lectin-ligand interactions in cell adhesion, cell recognition, and pattern formation in the early embryo; methods for bacterial and baculovirus expression. Conformations and dynamics of complex carbohydrates, free in solution and bound to lectins; ^{1}H-NMR methods to analyze the solution conformations and dynamics of oligosaccharides, glycopeptides, and glycolipids. Routine high-sensitivity and high-resolution analysis of oligosaccharides; capillary electrophoresis (CE) to identify structures of oligosaccharides of a glycoconjugate based on mobility; coupling CE to structural analysis methods.

Resource Capabilities

Instruments

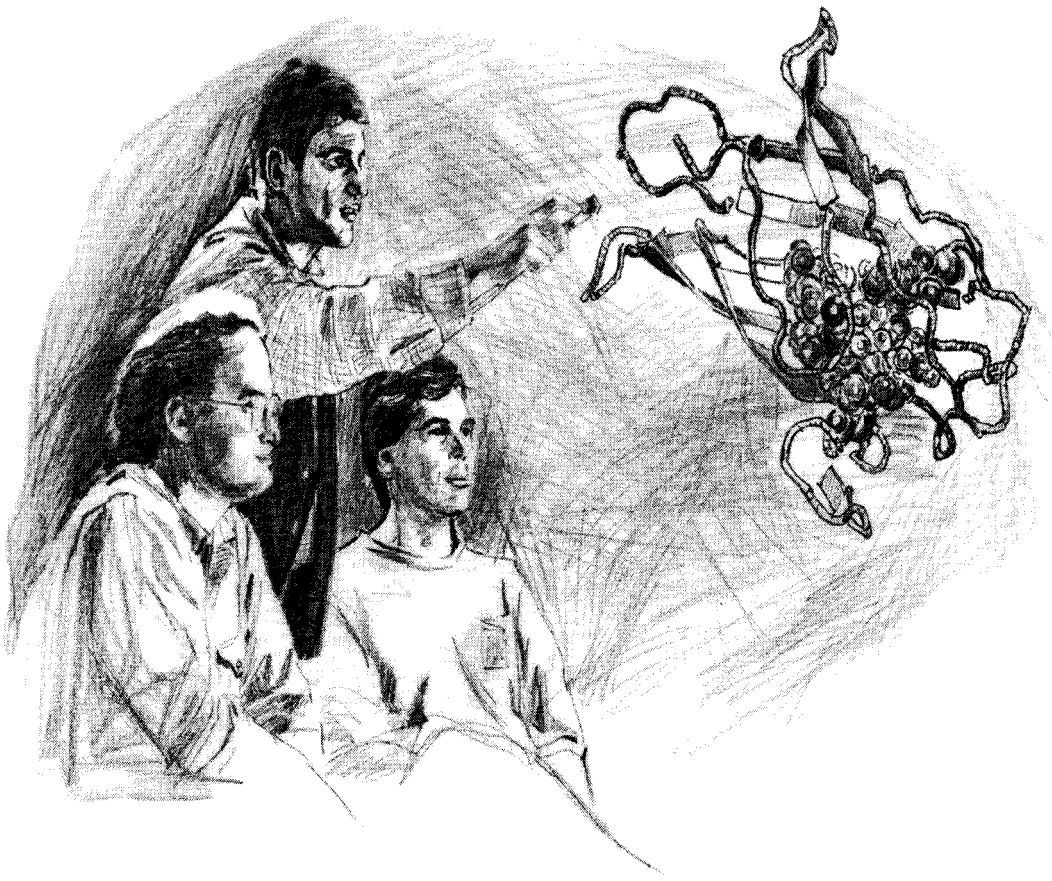
Varian FT-NMRs: Inova 800, Inova 600, Inova 500 wide-bore for liquids and solids; Mercury 300 spectrometers; PE-SCIEX API III electrospray, and JEOL JMS-SC1102/SXC102A four magnetic sector (with LC/MS interface) tandem, and HP 2030A LD-TOF mass spectrometers; HP 5985 GC/MS; and HP 5985 GC/MS; three HP mass selective detectors; Beckman P/ACE 2200 capillary electrophoresis system with laser-induced fluorescence detector; Dionex HPLCs; 12-processor SGI Origin 2000 and 4-processor Digital Alpha 2100 parallel servers.

Software

CCRC-Net, the Complex Carbohydrate Structure Database (CCSD/CarbBank), and databases of carbohydrate NMR and mass spectra all available at the center's Web site.

1. Lee, J.-K., Buckhaults, P., et al., Cloning and expression of the *Xenopus laevis* oocyte lectin and characterization of mRNA levels during early development. *Glycobiology* 7:367–372, 1997.
2. Brockman, A. and Orlando, R., New immobilization chemistry for probe affinity mass spectrometry. *Rapid Communications in Mass Spectrometry* 10:1688–1692, 1996.
3. Woods, R. J., The application of molecular modeling techniques to the determination of oligosaccharide solution conformations. In *Reviews in Computational Chemistry*, vol. 9 (K. Lipkowitz and D. B. Boyd, eds.). New York: VCH Publishers, 1996, pp. 129–165.
4. Yang, Y. and Orlando, R., Simplifying the exoglycosidase digestion/MALDI-MS procedures for sequencing *N*-linked carbohydrate side chains. *Analytical Chemistry* 68:570–572, 1996.

Isotopes and Particles



National Stable Isotope Resource at Los Alamos

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Research Emphasis

The technology research and development component of this resource is focused on the development and application of novel isotopic labeling strategies for biomedical research, with an emphasis on structural biology. An essential component is development of novel, efficient methods to synthesize ^{13}C, ^{15}N, $^{17,18}O$, $^{33,34}S$, and ^{77}Se-labeled compounds from ample materials such as H_2O, CO, NO, and H_2S. General procedures for synthesizing specific isotopomers of amino acids and nucleotides with particular labeling patterns are of major importance. Resource personnel will also synthesize specific labeled compounds for accredited investigators when these compounds are not readily available from commercial or other sources at acceptable costs. Resource staff collaborate with investigators, assist with NMR analysis and data interpretation, advise and assist in use of isotopes, and train in use of stable isotopes. The Resource also hosts visiting scientists and postdoctoral fellows and encourages exchanges of talks, short courses, and extended research opportunities.

Current Research

The current focus of the Stable Isotope Resource (SIR) core research is to develop efficient synthetic routes for labeled amino acids and nucleotides for applications in biomolecular structure and dynamics. Stable isotopes have properties that make them useful for a variety of spectroscopic techniques, including mass spectrometry, NMR ESR, and vibrational methods, particularly IR and Raman spectroscopy. Recent developments in these techniques have shown that they have unprecedented potential for studies of the structure and function of proteins, RNA, and DNA. Our ability to apply these techniques to important problems in biology depends on the availability of isotopically labeled compounds. The SIR is developing methods for site-specific labeling of amino acids and nucleotides that would be useful for mechanistic and dynamic studies of macromolecules. In addition, the SIR is developing methods for producing uniformly ^{15}N- and ^{13}C-labeled proteins and nucleic acids for NMR structural studies.

Resource Capabilities

Chemical materials: Separated ^{13}C, ^{15}N, and ^{18}O; labeled compounds that are not available commercially can be obtained on request.

1. Stocking, E. M., Schwarz, J. N., Senn, H., Salzmann, M., and Silks, L. A., Synthesis of (1)-Se-cystine, (1)-[77Se]-Se-cystine and (1)-Te-cystine. *Journal of the Chemical Society, Perkins Transactions* 1:2443, 1997.
2. Orji, C. C., Kelly, J., Ashburn, D. A., and Silks, L. A., The first synthesis of -2'-deoxy[9-15N]adenosine. *Journal of the Chemical Society, Perkins Transactions* 1:7:595–597, 1997.
3. Lodwig, S. N. and Unkefer, C. J., Stereoselective synthesis of stable isotope-labeled L-alpha-amino acids: Electrophilic amination of Oppolzer's acyl sultams in the synthesis of L-[^{15}N]alanine, L-[^{15}N]valine, L[^{15}N]leucine, L-[^{15}N]phenyl-alanine and L-[$^{1\text{-}13}C$, ^{15}N]valine. *Journal of Labelled Compounds and Radiopharmaceuticals* 38:239–248, 1996.
4. Silks, L. A., III, Dunkle, E., Unkefer, C. J., Sudmeier, J. L., Butler, M., and Bachovchin, W. W., A reinvestigation of the synthesis of [$^{15}N_2$]hydroxymethylimidazole: Useful in improved synthesis of (D,L)-[t, p-$^{15}N_2$]histidine. *Journal of Labelled Compounds and Radiopharmaceuticals* 36:947, 1995.

National Tritium Labelling Facility

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Research Emphasis

To safely produce tritiated compounds with very high specific activity and high chemical and radiochemical purity. The NTLF contains a unique combination of high-level labeling and analytical equipment dedicated to radiochemical analyses. Researchers participate in tritiation, purification, and analysis of their substrates. All major tritiation techniques are available: Hydrogenation, dehalogenation, methylation, acetylation, hydride reduction, and exchange. Labeled substrates containing one or more tritium atoms per molecule are produced routinely. High-performance liquid chromatography (HPLC) with radiochemical detection and other chromatographic techniques are used with tritium and proton nuclear magnetic resonance (NMR) spectroscopy to determine the extent and position of tritium incorporation. The hydride chemistry is not available commercially. Tritium NMR analyses of products are provided routinely.

Current Research

Current work is aimed at improving tritium labeling techniques, including the facile synthesis and use of highly tritiated hydride-reducing agents such as: LiEt3BT; LiA1T4; (Bun)3SnT; tritiated borane, LiT, and all the alkali metal borohydrides; tritiomethyl iodide; and tritioacetyl reagents at high specific activity. Other reactions are being developed for tritium labeling (desilylation, denitration, acid and base catalyzed exchange, electrophilic additions). Tritiated molecules prepared with these methods are being used to study chemical and biochemical processes. Chiral-labeled ethane has been used to look at the mechanism of oxidation of hydrocarbons by methane monooxygenase, with stereochemical analysis of products done by NMR. Isotope effects on kinetics of hydrogen transfer processes have been studied in porphyrins, and isotope effects on NMR chemical shifts are being used to study hydrogen bonding.

Tritium Labeling and Analysis Workshop

Each spring and fall the facility offers a 3-day workshop for four students, with lectures, two tritiation reactions, and analyses by liquid scintillation counting, gas-liquid chromatography (GLC), HPLC, and ^{3}H and ^{1}H NMR spectroscopy.

Resource Capabilities

Instruments

IBM AF-300, AMX-600, and GN-500 NMR spectrometers with 5 mm and 10 mm tritium probes; a Waters analytical HPLC system with Waters 996 photodiode detector and associated equipment; analytical HPLC system with Waters pumps, Hewlett Packard 1040A high-speed photodiode detector system with printer, plotter, integrator, floppy disks; IN/US β-RAM, IN/US Ramona and Berthold radioactivity flow monitors for HPLC; Varian 3700 GLC with heated proportional flow counter and associated electronics for multiscaling analysis; Hewlett Packard 8452A diode array UV/Vis spectrophotometer and Packard Tricarb model 1500 liquid scintillation analyzer; Hewlett Packard GC/MS.

1. Saljoughian, M., Morimoto, H., et al., N-tritioacetoxyphthalimide: A new high specific activity tritioacetylating reagent. *Journal of Organic Chemistry* 61:9625–9628, 1996.
2. Than, C., Morimoto, H., et al., Synthesis, NMR characterization, and a simple application of lithium borotritide. *Journal of Organic Chemistry* 61:8771–8774, 1996.
3. Than, C., Morimoto, H., et al., Tritium and deuterium labelling studies of alkali metal borohydrides and their application to simple reductions. *Journal of Labelled Compounds and Radiopharmaceuticals* 38:693–711, 1996.
4. Saljoughian, M., Morimoto, H., et al., Tritium labelled alkenes via the Shapiro reaction. *Tetrahedron Letters* 37:2923–2926, 1996.

Radiological Research Accelerator Facility

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Research Emphasis

The Columbia University Radiological Research Accelerator Facility (RARAF) is a dedicated facility for radiobiological research with ionizing radiations such as protons, alpha particles, and neutrons. RARAF is well established and highly user-friendly.

Current Research

The biological interest in the microbeam stems from the potential to define the ionizing energy absorbed by a cell, in terms of space, time, and number.

The microbeam allows irradiation of many cells each in highly localized spatial regions, such as part of the nucleus or cytoplasm, or of immediate neighbor cells of a given cell. This allows questions regarding cell-to-cell communication, functionality of subcomponents of the cell, and intracellular communication to be addressed directly.

At the low doses of relevance to environmental radiation exposure, individual cells only rarely experience traversals by an ionizing particle, the time intervals between the tracks typically being months. The biological effects of exactly one particle per cell are largely unknown because, due to the random distribution of tracks, they cannot be simulated in the laboratory using conventional broad-field exposures. Microbeam techniques overcome this limitation by delivering exactly one (or more) particle per cell nucleus.

Biological interest in the low-energy neutron facility stems from different mechanistic models of the effects of low doses of radiation make different predictions as to the effect of low-energy neutrons relative to fast neutrons. Thus low-energy neutrons, which produce nanometer-ranged proton recoils, are a unique mechanistic probe of the effects of energy deposition at the nanometer level.

The majority of the occupational radiation exposure to both airline personnel and nuclear-power workers is from low-energy neutrons. The relative biological effect of fast (MeV) neutrons is well understood; the relative effects of slow neutrons are not known.

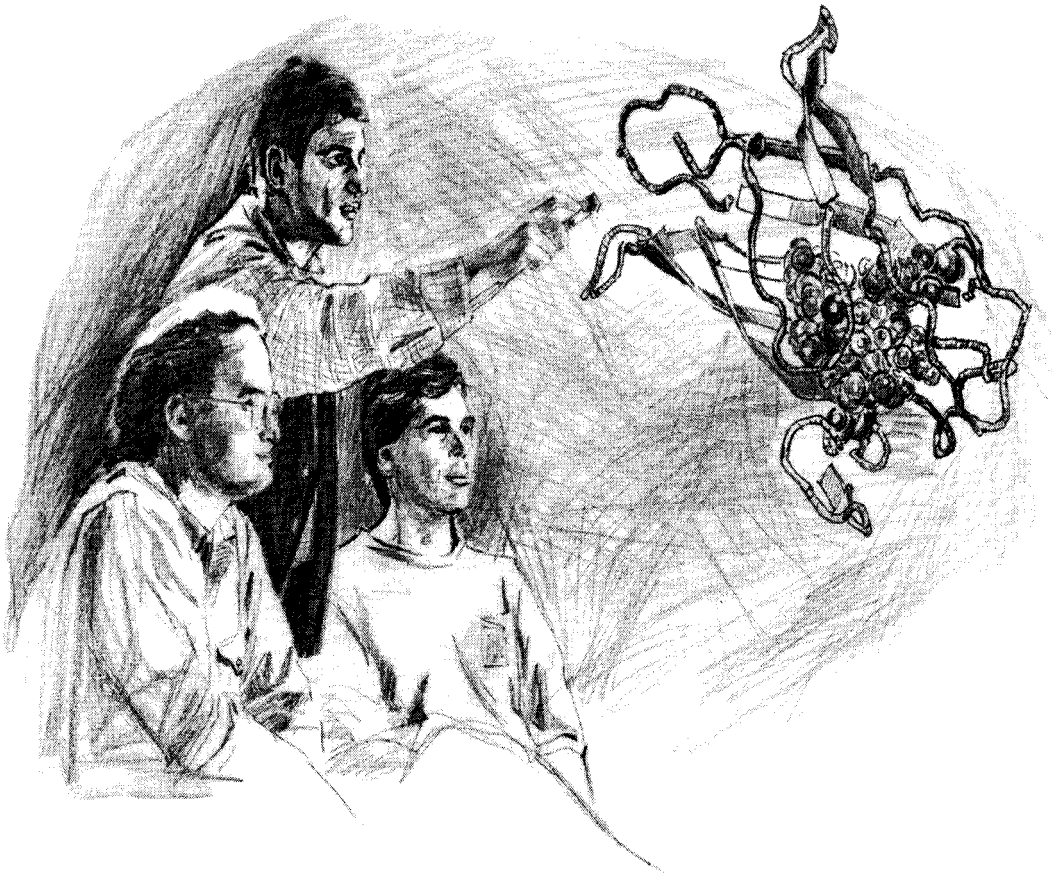
Slow (<50 KeV) neutrons are likely to be used increasingly in boron neutron capture therapy. The limiting normal tissue damage is from the soft neutrons themselves, the biological effectiveness of which is poorly known.

Resource Capabilities

A microbeam facility that delivers a predetermined number of charged particles (from one upward) in a given location through each of a number of cells growing on a dish. The goal is to attain a maximum throughput of ~10,000 irradiated cells/hr, and a maximum precision of ±1.5 µm, compared to the current capability of 1,700 cells per hour with a precision of ±5 µm. A further goal is to develop new optical cell-location systems that will include facilities for locating cells without use of fluorescent stain and UV exposure. A series of well-defined low-energy neutron beams (lowest dose-averaged mean energy <30 KeV) for biological research.

1. Geard, C. R., Randers-Pehrson, G., Hei, T. K., Jenkins, G. J., Miller, R. C., Wu, L. J., Brenner, D. J., Hall, E. J., Microbeam mediated cellular effects: Single alpha-particle induced chromosomal damage, cell cycle delay, mutation, and oncogenic transformation. *Transactions of the Faraday Society,* in press.
2. Hei, T K., Wu, L., Liu, S., Vannaist, D., Waldren, C. A., Randers-Pehrson, G., Mutagenic effects of a single and an exact number of a particles in mammalian cells. *Proceedings of the National Academy of Sciences USA* 94:3765–70, 1997.

Laser Applications



Center for Fluorescence Spectroscopy

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Research Emphasis

Time-domain (TD) and frequency-domain (FD) fluorescence methodologies to study the structure, function, and dynamics of biological macromolecules; time-resolved measurements of two-photon–induced fluorescence allows excitation of UV and visible fluorescence using red and NIR excitation wavelengths; development of long-lifetime metal ligand complex probes for use in biophysics and clinical chemistry and light quenching, a method to control excited data state population with nonabsorbed light pulses.

Current Research

Apply advanced fluorescence concepts and measurements in biochemical questions. Use fluorescence to quantify structural features of biological molecules, as revealed by distance distributions recovered from the time-resolved data. Anisotropy decays to study the hydrodynamics and internal dynamics of proteins and membranes. Time-dependent fluorescence quenching to determine the diffusion of small molecules within proteins and membranes. Two-photon excitation of fluorescence to obtain novel information from time-resolved fluorescence data and as basis for studies of two-photon fluorescence microscopy.

Resource Capabilities

Instruments

Both TD and FD instruments are available. FD measurements are provided from 100 KHz to 10 GHz, providing time resolution from the microsecond to picosecond timescales. The high-frequency measurements are possible as the result of custom circuits, developed by CFS staff, for use of high-speed microchannel plate detectors in FD instrumentation. TD measurements with 50 ps resolution are available using time-correlated single-photon counting. Both the TD and FD instrumentations are equipped with red-sensitive detectors, allowing their use in studies of time-dependent photon migration as well as biochemical fluorescence.

Novel instruments are under development for fluorescence lifetime imaging microscopy (FLIM). A FLIM instrument with a red-sensitive image intensifier will soon be available for photon migration imaging of tissues and turbid objects.

Software

Software for data analysis is available on-site or remotely over Internet, and runs on Silicon Graphics workstations. Many data analysis programs are also available on IBM PCs (386 or higher), but some programs involving diffusion or complex geometries require a workstation for reasonable execution time. A complete description of the CFS software is provided in the *CFS Software Manual*, which is available on request. Copies of individual programs, for use on PCs or workstations, can be obtained by contacting CFS staff.

1. Murtaza, Z., Chang, Q., Rao, G., Lin, H., and Lakowicz, J. R., Long-lifetime metal-ligand pH probe. *Analytical Biochemistry* 247:216–222, 1997.
2. Lakowicz, J. R., Gryczynski, I., Malak, H., Schrader, M., Engelhardt, P., Kano, I. L., and Hell, S. W., Time-resolved fluorescence spectroscopy and imaging of DNA labeled with DAPI and Hoechst 33342 using three-photon excitation. *Biophysical Journal* 72:567–578, 1997.
3. Gryczynski, I., Kusba, J., and Lakowicz, J. R., Wavelength-selective light quenching of biochemical fluorophores. *Journal of Biomedical Optics* 2(1):80–87, 1997.
4. Malak, H., Gryczynski, I., Dattalbaum, J. D., and Lakowicz, J. R., Three-photon-induced fluorescence of diphenylhexatriene in solvents and lipid bilayers. *Journal of Fluorescence* 7(2):99–106, 1997.
5. Burke, T. G., Malak, H., Gryczynski, L., Mi, Z., and Lakowicz, J. R., Fluorescence detection of the anticancer drug topetecan in plasma and whole blood by two-photon excitation. *Analytical Biochemistry* 242:266–270, 1996.

Developmental Resource for Biophysical Imaging and Opto-Electronics

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Research Emphasis

DRBIO focuses on creation of quantitative optical instrumentation for biophysical and biomedical research, including multiphoton fluorescence microscopy capable of intrinsic diffraction-limited 3-D resolved imaging of dynamic processes in living cells and thick tissue, photochemical micropharmacology by photoactivation of caged reagents, and dynamic supersensitive measurements at the single-molecule level. Simultaneous molecular absorption of multiple (2–4) infrared photons permits quantitative fluorimetric measurements involving standard biological probes and intrinsic cellular fluorophores. Research in photo-physical properties of fluorescent molecules undergoing multiphoton excitation provides the quantitative basis for biological applications. Optical force microscopy (OFM) uses optical tweezers and microinterferometry for surface scanning probe microscopy with piconewton force sensitivity. Measurements of intermolecular forces are possible in vitro. Nanometer tracking of individual macromolecules on cell surfaces has a 5 nm spatial sensitivity. Fluorescence correlation spectroscopy (FCS) measurements of the dynamics of diffusion, chemical kinetics, and protein folding provide single-molecule sensitivity in solution.

Current Research

We are developing instrumentation to extend imaging depth in thick living tissue preparations and optimize sensitivity to permit analytic imaging of intrinsic tissue autofluorescence with minimal photodamage. In situ photobleaching, phototoxicity, and induced fluorescence measurements discern the mechanistic aspects of photodamage. OFM measures binding forces between individual molecules at the piconewton level. FCS studies dynamic aspects of Green Fluorescent Protein. Multiphoton FCS measurements within cells are under development.

Resource Capabilities

Optical microscopy with support for image acquisition and data analysis. Simultaneous fluorescence microscopy and gigaseal patch clamp electrophysiology. Fluctuation analysis and spectroscopy. Optics and electronics for dynamic experiments on sparse molecular preparations. Cell culture and living tissue preparation facilities.

Instruments

Multiphoton laser scanning microscopes equipped with mode-locked lasers provide 100 fs pulses at 80 MHz with wavelengths tunable from 685 nm to 1050 nm for multiphoton imaging of UV and visible absorbing fluorophores. Inverted and upright microscopes equipped with electrophysiology (patch-clamping) equipment. Confocal laser scanning microscopes; microscopically resolved fluorescence emission spectroscopy; molecular diffusion measurements in two or three dimensions by fluorescence photobleaching recovery, fluorescence activation redistribution, and FCS; chemical kinetics by FCS with one- and two-photon excitation.

Software

A program for molecular recognition and nanometer molecular tracking is available via our Web page. Image acquisition and quantitative analysis software is facilitated through an ongoing collaboration with the NIH Parallel Processing Resource for Biomedical Scientists.

1. Stout, A. and Webb, W. W., Optical force microscopy. *Methodology of Cell Biology* 5:99–116, 1998.
2. Maiti, S., Haupts, U., and Webb, W. W., Fluorescence correlation spectroscopy: Diagnostics for sparse molecules. *Proceedings of the National Academy of Sciences USA* 94:11753–11757, 1997.
3. Maiti, S., Shear, J. B., Williams, R. M., Zipfel, W. R., and Webb, W. W., Measuring serotonin distribution in live cells with three-photon excitation. *Science* 275:530–532, 1997.
4. Xu, C., Zipfel, W., Shear, J. B., Williams, R. M., and Webb, W. W., Multiphoton fluorescence excitation: New spectral windows for biological nonlinear microscopy. *Proceedings of the National Academy of Sciences USA* 93:10763–10768, 1996.

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Research Emphasis

Developing real-time acquisition, in parallel, of emission spectra and wavelength-dependent fluorescence lifetimes in several instrumental modalities: Fluorescence lifetime detection for fluorescence microscopy (single- and two-photon excitation) and stopped-flow mixing; laser-based fluorescence correlation spectroscopy with two-photon excitation; pump-probe spectroscopy and microscopy; fluorescence spectroscopy in turbid media, such as tissue; software that allows tests of models that contain quenching, energy transfer, excited-state reactions, and other processes. Other software enables anisotropy decay analysis, including options for lifetime heterogeneity and distributions of lifetime values, a variety of rotator geometric shapes, and P2, P4 models; and global analysis of multiple fluorescence probes and time-resolved fluorescence decay.

Current Research

New instrumentation and methods to study cellular structure and function, fluorescence in tissue, and macromolecular dynamics and interactions. Studies of membrane fluidity and microdomains, internal protein motions, protein folding, protein-lipid interactions, protein subunit and protein-ligand interactions, DNA-protein and DNA-drug interactions, and the behavior of whole cells by observing changes in fluorescence lifetimes and rotation rates as a function of temperature, pressure, quencher concentration, and ligand or protein concentration. Physiological function of tissue based on variations of spectroscopic properties during optical imaging.

Resource Capabilities

Instruments

Time-resolved fluorescence instrumentation: Continuously variable frequency phase/modulation fluorometers with laser (titanium sapphire, argon ion, or synchronously pumped, cavity-dumped dye laser and mode-locked Nd/YAG) or xenon arc lamp sources provide excitation from the ultraviolet to the near infrared region; the sample compartment is thermostatted (-140°C to +70°C) and also accommodates high-pressure or gas-quenching vessels. A dedicated microcomputer also controls automation of mechanical and electronic functions. Faster time resolution by the pump-probe stimulated emission (microscope-based) apparatus. The fluorescence microscopes are adapted to fluorescence lifetime resolution and two-photon excitation, providing full-field and raster-scanning option, as well as particle tracking. Fluctuation correlation spectroscopy for low-concentration measurements of particle diffusion and self-association.

Steady-state instrumentation: Two photon-counting scanning fluorometers record emission/excitation spectra and polarization spectra as well as kinetics; the sample compartment is thermostatted and also accommodates the pressure and quenching vessels; a commercial spectrophotometer measures absorbance, percent transmission, and derivative spectra. A commercial circular dichroism polarimeter records spectra from 185 to 700 nm. A commercial stopped-flow mixer provides access to reaction rates of milliseconds with transmission and fluorescence (intensity, polarization, and lifetime) detection.

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2. Franceschini, M. A., Moesta, K. T., et al., Frequency-domain techniques enhance optical mammography: Initial clinical results. *Proceedings of the National Academy of Sciences USA* 94:6468–6473, 1997.
3. Masters, B. R., So, P. T. C., and Gratton, E., Multiphoton excitation fluorescence and spectroscopy of in vivo human skin. *Biophysiology Journal* 72:2405–2412, 1997.
4. Koenig, K., So, P. T. C., Mantulin, W. W., Tromberg, B. J., and Gratton, E., Two-photon excited lifetime imaging of autofluorescence in cells during UVA and NIR photostress. *Journal of Microscopy* 183:197–204, 1996.

Laser Biomedical Research Center

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Research Emphasis

Developing spectral diagnostic methods based on optical histochemical analysis for in vivo diagnosis of disease; understanding light propagation in turbid media; developing techniques for 3-D optical imaging of biological tissue; developing methods using near-infrared Raman spectroscopy for accurate concentration measurements of blood analytes including glucose, lactic acid, and creatinine; studying the physical processes involved in laser ablation of biological tissue; exploring the biophysics and biochemistry of biopolymer conformations and dynamics using laser light.

Current Research

Includes development of compact spectrometers and spectral endoscopes for use in a clinical setting. These systems are used to study reflectance, fluorescence, and Raman scattering from human tissues. Reflectance-based methods for in vivo diagnosis of precancerous lesions are being developed and tested in esophagus and colon tissues. Concentrations of blood analytes are being determined using near-infrared Raman spectroscopy and a new calibration technique called hybrid linear analysis. A prototype optical tomographic system that employs analysis of early arriving fluorescence photons is being developed. The thermo-acoustic response of soft tissues (such as meniscus) is being studied for developing diagnostic techniques in orthopedics.

Resource Capabilities

Instruments and Experimental Set-Ups

State-of-the-art facility for Raman spectroscopy in the near infrared, visible, and ultraviolet, with micro-Raman capability and fiberoptic probes for remote measurements; psec/fmsec laser system consisting of a mode-locked Ti:sapphire laser with second, third, and fourth harmonic generation, producing laser radiation in near infrared, visible, and ultraviolet; a streak camera capable of 2 psec resolution; fluorescence microspectroscopy; spectral endoscopes for fluorescence imaging of disease; excitation-emission matrix (EEM) spectrometer with multiwavelength excitation that collects an entire EEM in less than one second; time-correlated single photon counting system with an MCP photomultiplier tube for fluorescence decay measurements and time-resolved spectroscopy using dye lasers pumped by a mode-locked Nd:YAG laser; continuously tunable nanosecond-pulse radiation source, 216–4000 nm; FT-IR spectrometer with microscope accessory; conventional absorption spectrophotometer and spectrofluorometer.

1. Brennan, J. F., Romer, T. J., Lees, R. S., Tercyak, A. M., Kramer, J. R., and Feld, M. S., Determination of human coronary artery composition by Raman spectroscopy. *Circulation* 96:2834, 1997.
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Laser Microbeam and Medical Program

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Research Emphasis

Develop instrumentation and models to understand how light interacts with and propagates through cells/tissues.

Current Research

Optical visualization and manipulation tools (laser tweezers/scissors) combined with molecular methods (gene expression probes) to simultaneously visualize, inactivate, and activate cellular processes; biophysical mechanisms of inactivation and subcellular microablation. *Applications:* Monitoring/perturbing signal transduction, gene expression, and protein trafficking.

Mechanisms of coherent image formation; models to understand the origin and degradation of coherent light interactions in biological tissues; cellular pharmacokinetics, subcellular localization, and ligand-binding relationships for pharmacologically active therapeutics/probes. *Applications*: Monitoring/imaging hemodynamics before, during, and after interventional procedures.

Accuracy of tissue absorption and scattering measurements in complex, heterogeneous, biological systems; relationships between tissue optical properties and physiology/cellular structure; dynamic monitoring and mapping physiology and cellular structure in tissue phantoms, preclinical models, and human subjects. *Applications*: Lesion/tumor diagnostics in breast, brain, and cervix.

Resource Capabilities

Instruments

Confocal Ablation Trapping System: Integrates a trapping beam (CW Titanium:Sapphire laser) and ablation beam (Q-switched Nd:YAG with 2nd, 3rd harmonics) into a Zeiss laser scanning confocal microscope. Features up to two independently controlled optical trapping beams with a third independently controlled ablation beam. Detectors include a cooled color CCD camera and three-photomultiplier tubes. Confocal laser scanning with Argon or He:Ne laser excitation.

Optical Doppler Tomography: Optical fiber-based OCT system using superluminescent diode (P=1mW, λ_o=850 nm, $\Delta\lambda_{FWHM}$=25 nm) light source. Imaging in vivo blood flow and tissue structure simultaneously. Lateral and axial spatial resolution, determined by beam spot size and coherence length of light source, is 5 and 13 µm respectively. Velocity resolution is about 100 µm/s.

Two-Photon Microscope: A mode-locked, 150 fsec, 76 Mhz Ti: Sapphire source is modulated to reduce average power while preserving peak power at the sample. The excitation beam is scanned across the specimen on a modified Zeiss Axiovert 100 microscope. Two-photon fluorescence is detected using single-photon counting in up to 2 photomultiplier tube channels. Typical scans are 256 x 256 pixels in 1–2 seconds.

Frequency-Domain Photon Migration (FDPM): Multiwavelength, high-bandwidth (1 GHz) portable FDPM device for quantitative, noninvasive measurements of tissue optical and physiological properties. 300 kHz–1 GHz photon density waves (PDWs) are produced using up to 7 amplitude-modulated diode lasers (674–956 nm). The frequency-dependence of PDW phase and amplitude is measured and compared to analytically derived model functions in order to calculate absorption, μ_a, and reduced scattering, μ_s, parameters. The wavelength dependence of absorption is used to determine tissue hemoglobin concentration (total, oxy-, and deoxy- forms), oxygen saturation, and water concentration.

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2. Chen, Z., Milner, T. E., Dave, D., and Nelson, J. S., Optical Doppler tomographic image of fluid flow velocity in highly scattering media. *Optics Letters* 22:64–66, 1997.
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Research Emphasis

Development of methods for the investigation of ultrafast dynamic processes in proteins, enzymes, and nucleic acids; examples include electron and energy transfer in light-harvesting proteins, protein conformational changes, heme protein dynamics, photoisomerization in light-sensitive proteins, photophysics of single biomolecular assemblies.

Ultrafast (fs, ps, ns) methodologies are developed for these investigations: Time-correlated single-photon counting, transient spectroscopy (UV/Vis/vibrational IR/terahertz), photon echoes, two-photon absorption, laser-induced temperature jumps, femtosecond infrared methods, and time-resolved confocal microscopy.

Current Research

Ultrafast processes in liquids, molecular relaxation, and conformational change; protein and peptide folding; heme protein dynamics; electron transfer processes in reaction centers; excited state reaction dynamics (e.g., proton transfer); molecular motion in proteins; hemoglobin cooperativity; fluorescence of aromatic amino acids (e.g., tryptophan); and development of femtosecond laser methods; time-resolved spectroscopy of single molecules and far-infrared (terahertz) probing methods on biomolecules.

Resource Capabilities

Instruments

Femtosecond to nanosecond fluorescence spectrometers, femtosecond to millisecond transient absorption spectrometers using pulsed Nd:YAG, colliding pulse mode locked dye, and Ti:Sapphire lasers. Inverted confocal microscope with time-correlated single-photon counting and array detector capabilities.

Special Features

Instruments can rapidly record fluorescence in the range of 100 fs to many ns. Longer time needs are met by time-correlated photon counting and conversion methods for accurate subpicosecond fluorescence decays. Facilities are available for pump-probe experiments using a variety of optical wavelengths. Precision transient absorption spectra can be acquired in the fs to ms regime through the use of a low-noise, dual-diode-array spectrometer. Instrumentation has also been developed to perform transient IR and terahertz spectroscopy. Atomic force and confocal microscopes have been constructed that are investigating single molecules and molecular assemblies.

1. Volk, M., Kholodenko, Y., Lu, H. S. M., Gooding, E. A., DeGrado, W. F., and Hochstrasser, R. M., Peptide conformational dynamics and vibrational stark effects following photoinitiated disulfide cleavage. *Journal of Physical Chemistry B* 101:8607–8616, 1997.
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3. Bopp, M. A., Jia, Y., Li, L., Cogdell, R. J., and Hochstrasser, R. M., Fluorescence and photobleaching dynamics of single light-harvesting complexes. *Proceedings of the National Academy of Sciences USA* 94:10630–10635, 1997.
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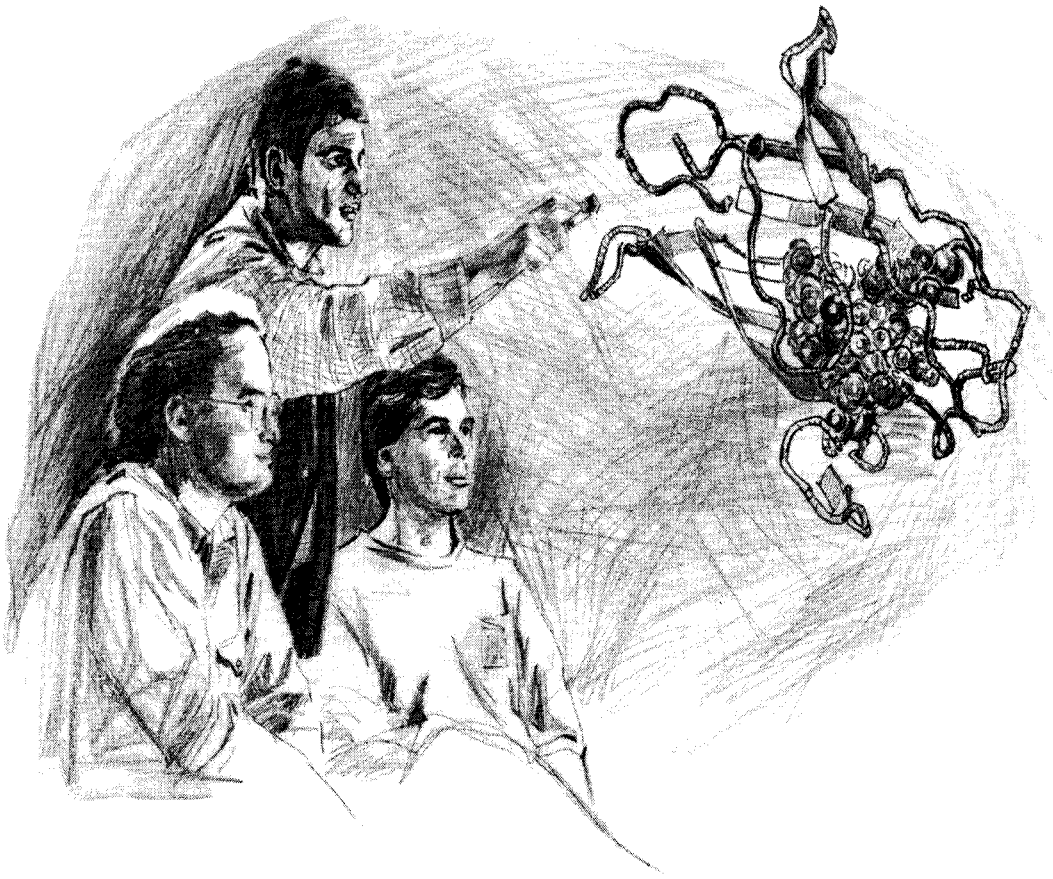
Magnetic Resonance Imaging (Structure and Function)



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Research Emphasis

The focus of this resource is on developing ultrahigh-resolution NMR microscopy and imaging, online data processing and interactive experimentation over the World Wide Web, magnetic contrast agents, spectra of small specimens, techniques for spectral localization, perfusion and diffusion measurements, and functional brain imaging.

Current Research

Microscopy, image processing and visualization, perfusion and diffusion measurements, new techniques for spectral localization, contrast agent development and characterization, microdomain techniques, retinal metabolism, muscle function, cold adaptation, thermotolerance, obstetrical/gynecological biopsy studies, labeling and tracking of neural cells, exercise effects on brain metabolism, and new methods for functional brain imaging.

Resource Capabilities

Instruments

SISCO 4.7 T/33 cm NMR imaging spectrometer with World Wide Web operating interface; GN300 Tecmag wide-bore multinuclear NMR spectrometer with microimaging; IBM Research field-cycling relaxometer; IBM PC/10 (Minispec) NMR analyzer; Varian 500 MHz narrow-bore multinuclear NMR imaging spectrometer with microimaging and World Wide Web operating interface; SMIS 4.0 T/31 cm NMR imaging spectrometer and SMIS 2.0 T/1 m NMR imaging spectrometer, both with real-time interactive virtual reality displays and operation over the World Wide Web.

Special Features

Microscopic probes for SISCO (developed in-house and Doty), 3-D FT and PR imaging and 4-D CSI. Fiberoptic link to National Center for Supercomputing Applications for image reconstruction and processing. Microsamples probe on GN300 developed on-site. Muscle force and length measurements in GN300 magnet. Microscope probe for GN300. Microscope probe (Doty) for Varian 500, RS/6000 computer for interactive control of SMIS 4.0 T/31 cm system. Ultramicroradiofrequency coils (as small as 5 micrometers) for scanning NMR microscopy. Probe for surface coil imaging of specimens on standard optical microscope slides.

1. Bruce, B. C., Carragher, B. O., Damon, B. M., Dawson, M. J., Eurell, J. A., Gregory, C. D., Lauterbur, P. C., Marjanovic, M. M., Mason-Fossum, B., Morris, H. D., Potter, C. S., and Thakkar, U., ChickScope: An interactive MRI classroom curriculum innovation for K–12. *Computers & Education Journal* 29:73–87, 1997 (special issue on multimedia-based learning).
2. Harrison, J. M., Liang, Z.-P., Magin, R. L., Duerk, J. L., and Lauterbur, P. C., A comparison of RIGR and SVD dynamic imaging methods. *Magnetic Resonance in Medicine* 38:161–167, 1997.
3. Kmiecik, J. A., Gregory, C. D., Liang, Z.-P., Hrad, D. E., Lauterbur, P. C., and Dawson, M. J., Quantitative lactate-specific MR imaging and spectroscopy of skeletal muscle at macroscopic and microscopic resolutions using a zero-quantum/double-quantum-coherence filter and SLIM/GSLIM localization. *Magnetic Resonance in Medicine* 37:840–850, 1997.
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5. Wiener, E. C., Auteri, F. P., Chen, J. W., Brechbiel, M. W., Gansow, O. A., Schneider, D. S., Belford, R. L., Clarkson, R. B., and Lauterbur, P. C., Molecular dynamics of ion-chelate complexes attached to dendrimers. *Journal of the American Chemical Society* 118:7774–7782, 1996.

Center for Advanced Magnetic Resonance Technology

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Research Emphasis

The mission of the Center for Advanced Magnetic Resonance Technology at Stanford is to develop innovative magnetic resonance (MR) techniques for fundamental anatomic, physiologic, and pathophysiologic studies involving animals and humans, and to serve the academic and scientific community through collaborations, education, and access to facilities and resources. Our core technology development encompasses these five areas:

Selective Excitation: Radiofrequency pulse design for single and multidimensional selectivity in both spatial and spectral domains. *Rapid Imaging Methods*: Spiral, fast spin echo, echo planar, and other variants that can be performed on conventional or high-performance imagers. *Imaging of Microvasculature*: Techniques for visualizing microvasculature (e.g., diffusion, perfusion, brain activation), include 2-D and 3-D spiral fMRI techniques and isotropic DWI. *Endogenous MR Contrast Mechanisms*: Blood oxygenation imaging, magnetization transfer, ^{1}H metabolite imaging, lipid-water imaging, short T_2 imaging and spectroscopy. *Quantitation and Imaging of Flow and Motion*: Techniques for visualizing and quantitating macroscopic spin motion (e.g., vascular imaging, flow measurement, and physiological motion analysis).

Current Research

Rapid Imaging: Spiral, EPI fluoro methods. *RF Pulses:* Spatially adaptive for shim correction. *Microvasculature:* Spiral BOLD and FAIR techniques, high-resolution, susceptibility artifact reduction. *Endogenous Contrast:* Oscillating gradient spectroscopy methods. *Quantitative Flow and Motion:* 3-D Cine MRA methods.

Resource Capabilities

Facilities

The Center is housed in the Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging, which has 15,000 square feet of space.

1.5 T GE Signa MR system (Rev 5.6) scanner with Echospeed gradients, broadband spectroscopy system and resistive shims interconnected to the host computer, Tardis memory with 256 MB of RAM, auxiliary disc drive to provide 700 MB of raw data file space and 400 MB for pulse sequences for researchers. Complete facilities for fMRI experiments, including three computers for stimulus generation and response recording, two video projectors, a VCR, an auditory presentation system, four channel fiber optic finger switch system, numerous stimulus systems including an 11 channel air valve system for air puff and pneumatic experiments, tactile stimulator, and multichannel olfactometer. Computer-controlled flow and motion phantoms. 4.7 T (@ 2.0 T) 40 cm Bruker (GE) CSI Omega MR system utilized for animal and in vitro research, with 20 g/cm shielded Acustar gradients. 3.0 T 80 cm GE Signa whole-body scanner laboratory under construction. Siemens Angiostar digital x-ray fluoroscopic/angiographic system; dry and wet lab space; surgical suite for preparation of animal models; Sun, SGI, and Mac computers with Matlab, IDL, and other software.

1. Glover, G. H. and Lai, S., Self-navigated spiral fMRI: Interleaved versus single-shot. *Magnetic Resonance in Medicine*, in press.
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4. Drangova, M., Zhu, Y., and Pelc, N. J., Effect of artifacts due to flowing blood on the reproducibility of phase-contrast measurements of myocardial motion. *Journal of Magnetic Resonance Imaging* 7:664–668, 1997.

Clinical MR Studies at 4.1 T: A Research Resource

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Research Emphasis

The focus of this high-field magnetic resonance resource is on developing new clinical biomedical applications with our 4 T imaging/spectroscopy system. These include high-resolution and functional imaging; high-resolution spectroscopic imaging in human brain, heart, and skeletal muscle; and the development of high-field and associated high-field, whole-body instrumentation methods for ^{1}H, ^{13}C, and ^{31}P turnover studies.

Current Research

Current efforts are focused on the development and application of methods for high-resolution functional imaging; high-resolution spectroscopic imaging of ^{1}H, ^{31}P, and ^{13}C metabolites in human brain, heart, and skeletal muscle; high-resolution neuroimaging; and development of new high-field, multiply tuned surface coils and volume resonators. These methods and hardware are being applied to study metabolic and anatomic alterations, including patients with ischemic heart disease, temporal lobe epilepsy, multiple sclerosis, cerebral ischemia, Alzheimer's disease, AIDS, and cardiomyopathies.

Resource Capabilities

Instruments

The resource contains a 4.1 T, 1 m bore NMR spectroscopy and imaging system. The system is equipped with a 25 mT/m shielded gradient system (68 cm id) and four 15 KW solid state amplifiers, covering the frequency range of 20–180 MHZ. It also contains two RF channels so that interleaved multinuclear and hetero- and homonuclear editing sequences can be implemented readily. A new Bruker console will allow more expeditious data acquisition. Data analysis is supported by six SunSPARC workstations with NMR1, SUNSPEC, SID, and PV WAVE. Modeling studies of the propagation of EM fields through human tissues from the coils developed is supported by a Hewlett Packard workstation utilizing software for 3-D solutions of Maxwell's equations. The facility is also equipped with two clinical 1.5 T, 1 m bore human systems, an 8.5 T, 9.8 cm bore and a 4.7 T, 40 cm bore animal system. Access to these systems is provided on a limited basis to support work on the 4.1 T system.

1. Chu, W. J., Hetherington, H. P., Kuzniecky, R. I., Simor, T., Mason, G. F., and Elgavish, G. A., Lateralization of human temporal lobe epilepsy by ^{31}P NMR spectroscopic imaging at 4.1 T. *Neurology*, in press.
2. Mason, G. F., Harshbarger, T., Hetherington, H. P., Zhang, Y., Pohost, G. M., and Twieg, D. B., A method to measure arbitrary k-space trajectories for rapid MR imaging. *Magnetic Resonance in Medicine* 38:492–496, 1997.
3. Doyle, M., Walsh, E. G., Foster, R., and Pohost, G. M., Common k-space acquisition: A method to improve myocardial grid-tag contrast. *Magnetic Resonance in Medicine* 37:418–424, 1997.
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5. Pan, J. W., Mason, G. F., Pohost, G. M., and Heatherington, H. P., Spectroscopic imaging of human brain glutamate by water-suppressed J-refocused coherence transfer at 4.1 T. *Magnetic Resonance in Medicine* 36:7–12, 1996.

Integrated Center for In Vivo Microscopy

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Research Emphasis

Developing magnetic resonance microscopy with a variety of pulse sequences at in-plane resolution to 10 μm: 3-D FT and projection acquisition of large arrays (256^3, 512^3); isotropic imaging; display and analysis for in vivo and fixed specimens; techniques to achieve microscopic ^{1}H imaging; and creative application to toxicology, tumor biology, embryology, histology, neurobiology, stroke, drug discovery, plant physiology, and marine science. Developments in hyperpolarized (HP) gas imaging are focused on models of pulmonary disease.

Current Research

Microscopic ^{1}H imaging; HP ^{3}He and ^{129}Xe gas imaging; and creative application to toxicology, tumor biology, embryology, histology, neurobiology, stroke, drug discovery, plant physiology, and marine science. Study of transgenic mice. Models of pulmonary disease.

Resource Capabilities

MR Microscopes

Three fully integrated MR systems are available, operating at 2.0 T (85 MHz), 30 cm horizontal bore; 7.1 T (300 MHz), 15 cm horizontal bore; and 9.4 T (400 MHz), 8.9 cm vertical bore. The 2.0 T and 7.1 T are supported by Sun-based consoles (Bruker, CSI consoles) with shielded gradients of 85 Gauss/cm each. A high-temperature superconducting probe in the 9.4 T system supports in-plane resolution of 10 μm for fixed specimens.

Computers

SPARC workstations, Power Macs, Silicon Graphics Reality Engine, Indigo^2, and O_2 power stations, optical disks, video production hardware, CD-ROM writer, laser and Codonics printer.

Software

Commercial, public domain, and in-house software permit special-purpose reconstruction using 3-D FT algorithms and projection reconstruction of multidimensional volumetric arrays (256^3 x 8 to 512^3). Analysis packages include quantitative calculation of spin density, T1, T2, diffusion coefficients, etc., from regions of interest or pixel by pixel. Volumetric packages allow interactive reformatting, visualization, and tissue volume quantitation. Animation software for video production and CD-ROM authoring.

Special Features

Physiological support and monitoring, cardiac and respiratory synchronization of small animals. RF coils constructed with on-site CAD, photolithography, and etching facilities. Laser gas polarizer for HP gas studies.

1. Delnomdedieu, M., Hedlund, L. W., Maronpot, R. R., and Johnson, G. A., MR microscopy and histopathology: Comparative approach to bromobenzene-induced hepatoxicity in the rat. *Hepatology*, in press.
2. Qiu, H., Hedlund, L. W., Neuman, M. R., Edwards, C. R., Black, R. D., Cofer, G. P., and Johnson, G. A., Measuring the progression of foreign body reaction to silicone implants using in vivo MR microscopy. *IEEE Transactions in Biomedical Engineering*, in press.
3. Chen, X. J., Chawla, M. S., Hedlund, L. W., Moller, J. R., MacFall, H. E., and Johnson, G. A., MR microscopy of lung airways with hyperpolarized ^{3}He. *Magnetic Resonance in Medicine* 39:79-84, 1998.
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Research Emphasis

The focus of this resource is on developing methodologies for the acquisition of morphological, biochemical, and functional information in living animals using nuclear magnetic resonance (NMR) imaging and spectroscopy. Novel techniques utilizing multinuclear NMR imaging, microimaging, and multinuclear in vivo spectroscopy are being applied to a wide range of problems in the biomedical sciences.

Current Research

Application of NMR imaging and spectroscopy to the study of biomedical problems using animal models. Development of new methodology in NMR imaging and spectroscopy.

Resource Capabilities

Instruments

Bruker BIOSPEC Avance 4.7 T, 40 cm NMR spectrometer with actively shielded gradients; Bruker BIOSPEC Avance 7.0 T, 15 cm NMR spectrometer with microimaging accessories; 2.35 T, 31 cm NMR spectrometer; Bruker DRX Avance-300 (wide bore), DRX Avance-500, and two DRX Avance-600 (vertical bore) NMR spectrometers.

Special Features

Facilities for performing NMR experiments on living animals.

1. Forbes, M. L., Hendrich, K. S., Kochanek, P. M., Williams, D. S., Schiding, J. K., Wisniewski, S. R., Kelsey, S. F., DeKosky, S. T., Graham, S. H., Marion, D. W., and Ho, C., Assessment of cerebral blood flow and $C0_2$ reactivity after controlled cortical impact by perfusion magnetic resonance imaging using arterial spin-labeling in rats. *Journal of Cerebral Blood Flow and Metabolism* 17:865–874, 1997.
2. Lin, Y. J. and Koretsky, A. P., Manganese ion enhances T1 weighted MRI during brain activation: An approach to direct imaging of brain function. *Magnetic Resonance in Medicine* 38:378–388, 1997.
3. Yeh, T. C., Zhang, W., Ildstad, S. T., and Ho, C., In vivo dynamic MRI tracking of rat T-cells labeled with superparamagnetic iron-oxide particles. *Magnetic Resonance in Medicine* 33:200–208, 1995.
4. Zha, L. and Lowe, I. J., Optimized ultra-fast imaging sequence (OUFIS). *Magnetic Resonance in Medicine* 33:377–395, 1995.

NMR Imaging and Localized Spectroscopy at High Magnetic Fields

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Research Emphasis

The focus of this resource is on developing high-resolution and high-contrast anatomic images of the human brain; functional images of the human brain for sensory and cognitive tasks; localized spectroscopy in humans; adiabatic pulses for imaging and multinuclear spectroscopy; and improved methods for chemical shift imaging, functional imaging, and single voxel localized spectroscopy.

Current Research

Functional imaging in the human brain; mechanisms of functional contrast applications of functional imaging in the human brain to the motor cortex, the visual system, and cognitive tasks. Development of high-contrast and high-resolution anatomical imaging at high magnetic fields, development of B_1 insensitive imaging approaches. Development of new and novel B_1 insensitive adiabatic pulses for spectroscopic and imaging applications using coils that are intrinsically inhomogeneous in their RF field profiles, such as surface coils. Spectroscopic localization techniques, spectroscopic editing techniques combined with spectroscopic localization, multiple quantum techniques. Improved methods for chemical shift imaging.

Resource Capabilities

Instruments

4 tesla/125 cm bore magnetic resonance imaging and spectroscopy instrument by SIS/Siemens. SunSPARC 10-30, 10-40 computers, RF analysis and test equipment. Radiofrequency probes designed for human applications at high frequencies, ultra-quiet reamplifiers for high frequencies to be coupled with RF coils.

Special Features

4 tesla human system represents the highest magnetic field available for humans at the present time.

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Research Emphasis

The focus of this resource is on developing instrumentation, methodologies, and data analysis for in vivo monitoring of specific metabolites in localized regions of tissues and organs in humans, utilizing multinuclear magnetic resonance spectroscopy; and novel spectral functional and perfusion imaging techniques. Versatile in-magnet exercise apparatus and monitoring equipment and extensive computer facilities for modeling and analysis are available. Methods for quantitative localized spectroscopy and specialized pulse shape synthesis, localized spectral editing, and polarization transfer are also provided.

Current Research

Proton MR of deoxymyoglobin for monitoring muscle oxygenation levels, evaluation of metabolic recovery from acute exercise, and blood flow properties in large vessels, spatial localization techniques, and data analysis. Development of targeted magnetite-based contrast agents for gene therapy and diagnosis. Development of techniques for near-infrared optical imaging and spectroscopy in humans.

Resource Capabilities

1-meter bore, 2.0 tesla NMR magnet giving ^{1}H at 85.4 MHz; ^{31}P at 34.5 MHz with a versatile spectrometer for multinuclear spectroscopy and imaging; specialized probes for various nuclei; local magnetic field gradient sets; workstations for separate data analysis; electronic test equipment; physiological monitoring equipment; in-magnet exercise apparatus; and bioelectric amplifiers and recorders.

Metabolic spectroscopy including (but not limited to) ^{1}H, ^{13}C, ^{15}N, ^{23}Na, ^{7}Li, ^{19}F, and ^{31}P; equipped for physiological synchronization (gating) and decoupling, magnetization transfer experiments, 2-D spectroscopy, and in-magnet exercise. Current software capabilities include automatic shimming, automatic phase optimization, and accurate real-time phase calculations. Software and hardware support almost all NMR experiments, including sodium and phosphorus imaging, chemical shift imaging, Hadamard spectroscopic imaging, and high-resolution proton imaging and flow. Facilities and expertise for specialized coil design and construction are available, as are body-positioning devices for specific experiments (i.e., in-magnet exercise; heart, brain, and liver studies).

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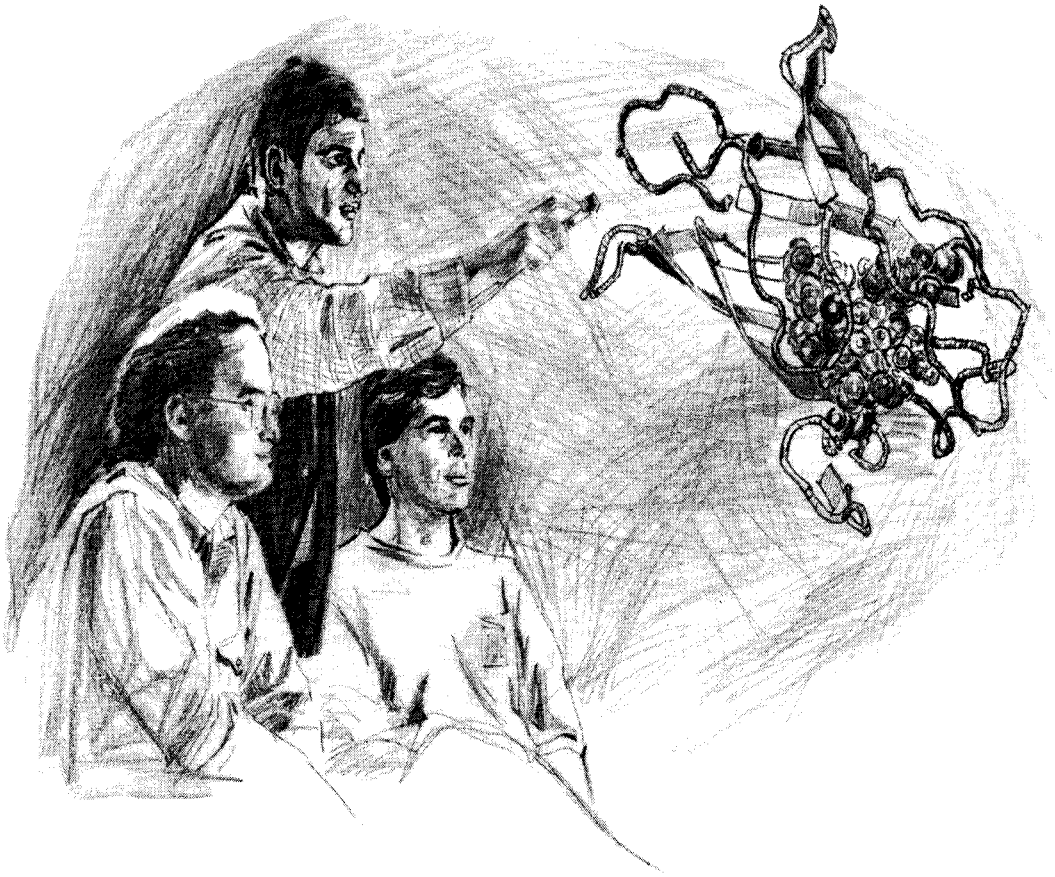
Magnetic Resonance Spectroscopy



Biotechnology Resource in Pulsed EPR Spectroscopy

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Research Emphasis

Measuring hyperfine and superhyperfine interactions between magnetic nuclei and paramagnetic centers through the use of electron spin echo (ESE) envelope modulation techniques and electron-nuclear double resonance (ENDOR) spectroscopy. Both ESE and ENDOR relate observed spectroscopic splittings to nuclei identity, and can quantify the magnetic coupling between those nuclei and the paramagnet. These coupling parameters characterize ligand bonding and the distance of a ligand nucleus from the paramagnetic center and the relative orientation of a ligand molecule with respect to a structural component of the paramagnetic center. ESE envelope modulation studies show ligand group identity and the number of such ligands bound. These studies can yield much information concerning the structure surrounding a paramagnetic center and how that structure is altered by chemical or biochemical processes. Linear electric field effect (LEFE) measurement using the ESE technique provides information concerning crystal field symmetry for paramagnetic metalloproteins, metal complexes, and transition metal model compounds.

Current Research

ESE envelope modulation studies of metalloproteins, metal-drug complexes, transition metal model complexes, and radical species of biological importance, including single crystal studies. Ligation structure surrounding paramagnetic metal centers in biomolecules and how those structures change when various substrates or inhibitors are added. Model compound studies on providing the framework for interpreting protein data and understanding ESE envelope modulation data from first principles. Development of computer software for analysis of these data for the study of biological materials.

Resource Capabilities

A pulsed EPR spectrometer for performing ESE experiments over a microwave frequency range of 8–18 GHz with a 1 KW microwave pulse power amplifier, capable of delivering minimum pulse widths of 10 ns; a Varian E-112 cw EPR spectrometer operating at X-band; and a Bruker ER 200 D X-band cw EPR spectrometer with an EN-810 ENDOR accessory. Special features of the pulsed EPR instrument are cryogenic measurements to 1.3 K, pulse programmer time resolution of 1 ns, up to six programmable pulses, equipment for performing LEFE and electron spin echo ENDOR measurements, stripline and folded stripline cavities to accommodate samples in 4 mm O.D. quartz tubes, cavities for single crystal EPR and ESE. Silicon Graphics Indigo^2 and MicroVAX II workstations for data analysis including fast Fourier transformation and simulation of ESE envelope modulation data. A standard biochemical lab with extensive equipment for sample preparation and characterization, a Perkin-Elmer 5000 atomic absorption spectrometer, an Aviv Model 14DS UV-Vis-IR spectrophotometer, centrifuges, and a cold room.

Computer software for the theoretical simulation of EPR, ENDOR, and ESE spectra of single crystals, powders, and liquids, with the ability to choose spectral parameters for the best fit between theoretical and experimental data. Some ENDOR and ESEEM software programs . Simulations for anisotropic g, A, and Q. Data transfer to other laboratories via BITNET.

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Research Emphasis

The focus of this resource is the development and application of state-of-the-art instrumentation for high-field NMR and EPR investigations of diverse biological systems including soluble and membrane proteins, nucleic acids, lipids, cells, tissues, intact organs, and animals. The experimental facilities include: High-resolution spectrometers for solution NMR operating between 360 and 750 MHz with capabilities of triple resonance gradient experiments; solid-state spectrometers in the 200–500 MHz range with magic angle spinning to 20 KHz and down to temperatures of 20 K; a CW and pulsed EPR spectrometer operating at 140 GHz, with TE001 cylindrical resonators; imaging spectrometers at 100–200 MHz.

Major research efforts are concerned with structures of membrane proteins, soluble proteins, RNAs, EPR and solid-state NMR of transient intermediates in biochemical reactions, imaging with RF gradients, high-frequency NMR microscopy, and spectroscopy of a variety of animal systems.

Resource Capabilities

Additional Features

Low-temperature (77 K), high-speed, triple-resonance MAS probes and triple-resonance gradient probes for solution experiments; probes for EPR at 140 GHz down to 4.2 K; computers available for data processing include: Two Digital AlfaStation 400 4/233, one Digital Alfa DEC 3000, one Digital VaxStation 4000/90, one Silicon Graphics Indigo^2, one Stardent 3000 graphics minisupercomputer with BIOGRAF for molecular modeling, access to the MIT Supercomputer Center. For data acquisition, three Digital AlfaStation 2200 4/100. Hewlett Packard Draftmaster III 48" x 36" plotter.

Software for NMR data processing includes FELIX 230, NMR Workbench, NMR Compass, NMR Toolkit, NMR1, NMR2, RNMR for acquisition and processing. XPLOR, QUANTA, CHARMm, INSIGHT, DISCOVER, and CATALYSIS R3 are available for molecular modeling/structure determination.

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EPR Center for the Study of Viable Systems

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Research Emphasis

The focus of this resource is the development and application of techniques that make it feasible to carry out well-resolved EPR spectroscopy in fully functional living systems. This includes studies in living animals (with or without anesthesia) and in viable cells. Developments under way include techniques to extend these capabilities to large animals and human subjects. The parameters that are measured by these techniques include the partial pressure of oxygen; oxygen consumption; and distribution and metabolism of paramagnetic species including nitroxides, free radical intermediates of drugs, spin trapping, and paramagnetic metal ions.

Current Research

The Center especially features techniques to measure the pO_2 in vivo repeatedly and accurately for investigation of tumors and ischemic diseases; the use of in vivo EPR for pharmacological studies; the measurement of reactive species (including nitric oxide) in vivo; and the measurement of oxygen, nitric oxide, and oxygen consumption in cells.

Resource Capabilities

For in vivo EPR these include two 1.2 GHz frequency ("L-Band") EPR spectrometers optimized for use in the presence of physiological motions, a wide range of resonators adaptable for specific types of investigations, and physiological monitoring equipment consistent for use with in vivo EPR.

For EPR studies of cell systems there are two 9 GHz EPR spectrometers ("X-Band") with supporting equipment to facilitate physiological control of temperature, oxygen, etc.

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3. Jiang, J., Liu, K. J, Shi, X., and Swartz, H. M., Detection of short-lived free radicals by low frequency ESR spin trapping in whole living animals: Evidence of sulfur trioxide anion free radical generation in vivo. *Archives of Biochemistry and Biophysiology* 319:570–573, 1995.
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Research Emphasis

Multifrequency electron paramagnetic resonance (EPR, also called electron spin resonance [ESR] or electronic magnetic resonance [EMR]) from <1 to >100 GHz, providing an experimental route to probe electronic structure molecular interactions, distances, motion, and molecular environments. Techniques combining EPR and NMR methods—electron-nuclear double resonance (ENDOR), pulsed EPR including 2–4 GHz electron spin echo envelope modulation (ESEEM), and low-field dynamic nuclear polarization (DNP). EPR biosensors to probe oxygen, nitric oxide, and free radicals in animal tissues, cells, and membranes.

Current Research

Applications of EPR to biological systems from single cells to animals; characterization of metalloproteins including those with integer spin metal ions like Fe[II]; EPR oxygen and nitric oxide sensors; high-frequency (HF) EPR (e.g., resolution of spin-trap adducts, study of molecular dynamics and partitioning in model biological membranes, and protein folding/unfolding study by site-directed spin labeling and high-frequency EPR); local order in disordered materials (powders, glasses, frozen solutions, polymers) by ENDOR, ESE, DNP, and HF EPR spectroscopies; low-frequency ESE; EPR study of paramagnetic contrast agents for MRI; predictive theory of relationship between structure and HF EPR spectra, e.g., of semiquinones or spin labels; spectral simulation and fitting strategies.

Resource Capabilities

Instruments

EPR spectrometers operating at 1–2 GHz, 2–4 GHz, 35 GHz, and 95 GHz. Digitally controlled instrumentation for experimental control and data acquisition. Variable sample temperature (2.5 to 473 K, available range dependent on specific spectrometer required). Parallel-field cavity at 9.5 GHz. ENDOR at 9.5 GHz. Two high-frequency (ca. 94 GHz) EPR spectrometers with superconducting magnets, offering wide-sweep (0 to 7 T) or fine sweep (0.03 T or 0.12 T ranges), low-temperature, sample rotation, and microsample (submicroliter) capabilities. 2–4 GHz pulsed EPR spectrometer. 1–2 GHz EPR surface probes suitable for monitoring signals at small (0.5–1 cm) depths in animals or materials. DNP relaxometer at 100 G. Spectral simulation and fitting capabilities. Access to SQUID magnetometer. Cell culture facilities.

Special Features

An anonymous FTP site (ftp to ierc.scs.uiuc.edu; log in as "anonymous" with your full e-mail address as the password, and read file "README.1ST" or through WWW at http://ierc.scs.uiuc.edu/) with EPR-related software to be downloaded. An EPR newsletter (open http://ierc.scs.uiuc.edu/news.html) with the International EPR (ESR) Society (open http://ierc.scs.uiuc.edu/IES.html). Service on samples submitted for investigation. Individual student or postdoctoral traineeships, typically 1–3 weeks long.

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Research Emphasis

Development of a multiquantum X-band spectrometer, development of loop-gap resonators, applying multifrequency electron paramagnetic resonance (EPR) to characterize paramagnetic centers, study of relaxation processes using multifrequency pulse saturation recovery, use of nitroxide radical spin labels to measure translational and rotational diffusion in biological systems, site-directed spin labeling (SDSL), and use of EPR for the detection of nitric oxide and oxy radicals.

Current Research

Physical studies of nitroxide radical spin labels, measurement of spin-label T_1s, diffusion processes in synthetic and biological membranes, measurement of oxygen concentrations in synthetic membranes and oxygen uptake in cellular systems, EPR characterization of immobilized free radicals, structure of ferric enterobactin receptor, FepA, and also the lens protein crystallin using SDSL methods, oxidation mechanisms and toxicity of catecholamines, spin trapping and spin stabilization of oxygen-centered free radicals, spin-trap assays for nitric oxide, copper ligation and charge in copper proteins and copper-containing chemotherapeutic and radiosensitizing drugs, and characterization of higher-order effects occurring in transition metal spectra measured with lower frequency microwaves.

Resource Capabilities

Instruments

Two Varian E-109 EPR spectrometers, ELDOR (Varian E-9 EPR spectrometer with E-800 frequency-swept ELDOR accessory), multifrequency EPR (0.5–1 GHz, 1–2 GHz, 2–4 GHz, 4–8 GHz, 9 GHz, 19 GHz, and 35 GHz bridges), X-band multiquantum spectrometer, time-domain EPR (saturation-recovery measurements of relaxation times) at 2–5 GHz, 9 GHz, and 19 GHz, IBM Instruments ER-200D EPR spectrometer system. Numerous loop-gap resonators for special experiments. Magnetometers and frequency counters available for precise field and frequency measurements (including 35 GHz).

Special Features

Extensive cryogenic equipment including liquid helium apparatus for all available microwave frequencies, computers for data acquisition and spectral simulation, Hewlett Packard 735 work station with high-frequency structure simulator and microwave design software, vacuum line, photochemical facilities including Xe and Hg lamps and monochrometer, Update Instruments stopped flow EPR apparatus, Hewlett Packard HP8452 diode array spectrophotometer, Sorvall RC5B super-speed refrigerated centrifuge, Beckman Model 167 HPLC, Hewlett Packard series 1050 HPLC, ABI 310 genetic analyzer, Insight II Molecular Modeling Environment, and other routine chemical and biological laboratory equipment. Microwave test equipment including Hewlett Packard Network Analyzer (8510) to 20 GHz and Spectrum Analyzer (8566B). Hewlett Packard Network Analyzer, 5 Hz to 200 MHz.

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Research Emphasis

A major focus is on developing multinuclear, multidimensional NMR approaches to solution-state studies of biological macromolecules, such as proteins, nucleic acids, carbohydrates, and lipids. Related collaborative projects converge on structure-function investigations of proteins and nucleic acids. The resource has considerable experience in labeling proteins with stable isotopes and in studying binding equilibria, conformational equilibria, internal mobility, and protonation steps in proteins. Proteins containing paramagnetic centers are a specialty. Instrumentation developed here extends data collection to high pressures so both pressure and temperature can be thermodynamic variables in NMR investigations. Software developed in the resource and available to users includes packages for maximum likelihood ("least squares") analysis of NMR data, analysis of NMR data relevant to conformational averaging, and automated assignment of protein NMR spectra.

A longer term goal is to simplify and automate procedures used in determining NMR structures of proteins and in studying properties related to their function. The resource also supports collaborations and user projects on microimaging and noninvasive analysis of the biochemistry of intact cells, tissues, organs, and intact living organisms.

Resource Capabilities

Five NMR spectrometers are available for data collection: One 400 MHz, two 500 MHz, one 600 MHz, and one 750 MHz (^{1}H frequency). Sample probes include: Triple-resonance probes with three-axis gradients (5 mm) available on all spectrometers, a quadruple-resonance probe (^{1}H, ^{13}C, ^{15}N, ^{31}P with ^{2}H lock), large (8 mm) and small (2.5 mm) diameter triple-resonance probes with single-axis gradient, several inverse and direct observe variable frequency probes, whole-animal probe with surface coil. Resource-built probes have been developed for perifusion of tissue samples, perfused organs, and high-pressure NMR. A server and network of computer workstations are equipped with a wide range of software packages relevant to NMR spectroscopy and structural biology. See the NMRFAM Web site for complete details on the current status and specifications of equipment.

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Resource for Solid-State NMR of Proteins

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Research Emphasis

The Resource is highly focused on the development and application of solid-state NMR spectroscopy for structure determination of peptides and proteins, especially those that can be prepared in forms suitable for x-ray crystallography or multidimensional solution NMR spectroscopy. The instrumentation includes two high-field NMR spectrometers built in-house capable of the full range of multiple-pulse and multiple-resonance solid-state NMR experiments. All spectrometers are equipped for magic angle sample spinning experiments, but the emphasis is on methods that utilize mechanically or magnetically oriented samples. The development encompasses the preparation of samples, including expression and purification of polypeptides, design and construction of instrumentation, especially probes, and the implementation of new pulse sequences for solid-state NMR spectroscopy. The applications are primarily to membrane-associated peptides and proteins.

Current Research

Most of the current research projects, including those of the core, collaborative, and service research activities, involve the determination of the three-dimensional structures of membrane proteins. Methods and instrumentation are being developed so that it is possible to completely resolve and assign multidimensional solid-state NMR spectra of uniformly labeled peptide in membrane bilayers. These experiments lend themselves to measurements of spectral parameters from the operative ^{1}H, ^{13}C, and ^{15}N spin-interactions that are orientationally dependent. Systems currently under investigation include ion channel peptides and proteins, Vpu from HIV-1, merT from the bacterial mercury detoxification system, colicin, recoverin, and a variety of membrane-associated peptides.

Resource Capabilities

The principal instruments are two high-field NMR spectrometers built in-house. One has a wide bore (89 mm) magnet operating at a field corresponding to a ^{1}H resonance frequency of 550 MHz. The second spectrometer has a mid-bore (62 mm) magnet operating at a field corresponding to a ^{1}H resonance frequency of 700 MHz. These instruments are supplemented by two other solid-state NMR spectrometers with wide bore magnets operating at fields corresponding to ^{1}H resonance frequencies of 360 MHz and 400 MHz. All of the spectrometers are capable of demanding solid-state NMR experiments at very high powers and are equipped with a wide variety of custom and commercial probes. An important component of the Resource is an electronics shop that is fully equipped for the design and construction of all components of NMR spectrometers and probes.

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Research Emphasis

The Facility's core research efforts focus on three projects. The first is to develop and refine the use of ^{13}C NMR isotopomer analysis for the investigation of intermediary metabolism in intact, functioning tissues, and to apply these methods to current questions in metabolism. Techniques to assess human hepatic metabolism by ^{13}C NMR of body fluids following ingestion of stable carbon isotopes and metabolite-conjugation agents have been developed.

The second project aims to develop and refine mathematical models to estimate the flux through different metabolic pathways using isotopomer analysis of ^{13}C NMR and/or mass spectroscopy (MS) data. Three programs are under development: tcaSIM, a simulation of the tricarboxylic acid (TCA) cycle that generates ^{13}C isotopomer data for use in the design of experiments; tcaCALC, a model that estimates relative pathway fluxes from NMR spectra or MS data obtained at metabolic and isotopic steady state; and tcaFLUX, a kinetic analysis that allows measurement of absolute flux from systems at metabolic, but not isotopic, steady state. tcaSIM and tcaCALC are available free of charge to researchers.

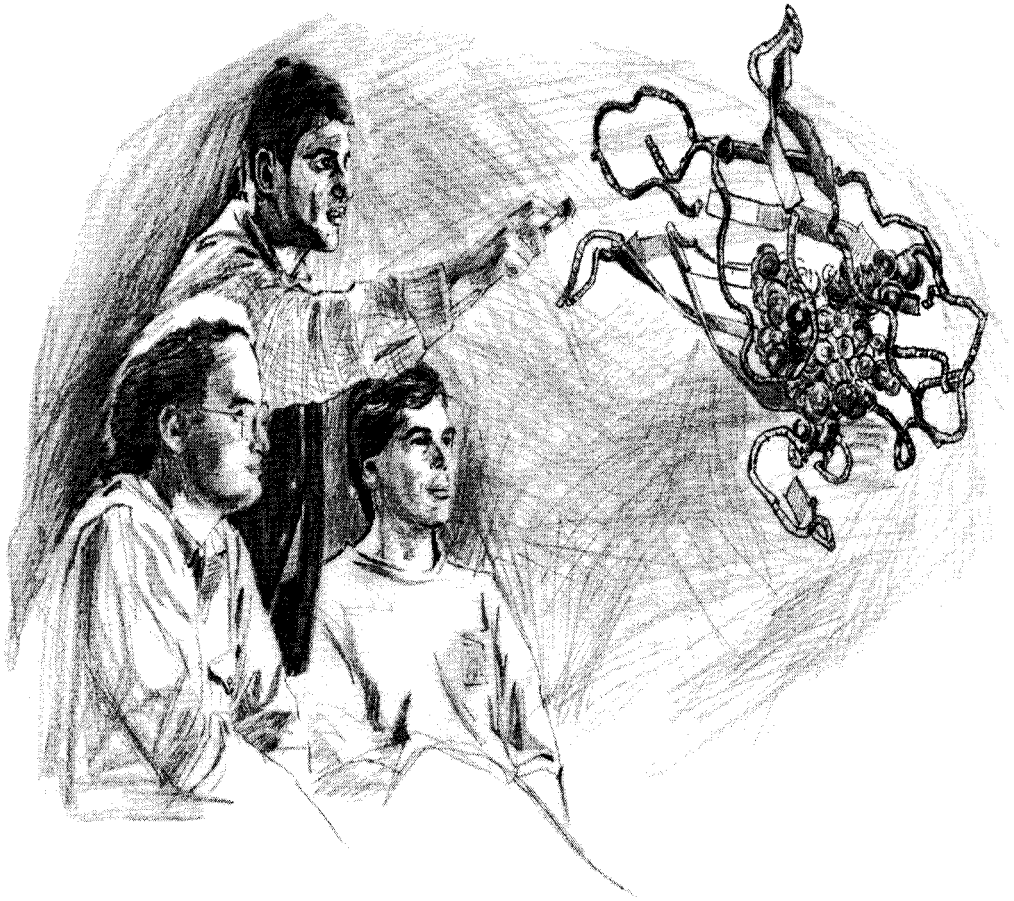
The third project aims to develop new techniques and agents for monitoring intercellular cations, particularly sodium, magnesium, and calcium, in perfused tissues and in vivo. Synthetic chemistry and characterization of new agents is ongoing at the University of Texas at Dallas. Evaluation and application of the new agents for perfused organ and in vivo studies is carried out at the Rogers MR Center at the UT Southwestern Medical Center.

Resource Capabilities

A range of NMR instruments (200, 300, 400, 500, and 600 MHz, including vertical and horizontal bore systems) is available with capabilities for both gradient-based experiments (imaging, spatially localized spectroscopy, metabolite-specific spectroscopy) and standard spectroscopy (decoupling, magnetization transfer, multiple quantum, 2-D). A bench-top gas chromatograph–mass spectrometer capable of tandem MS complements the NMR data and provides an additional approach to ^{13}C isotopomer analysis. Special expertise is available in isotopomer analysis of ^{13}C NMR spectra, working heart perfusion preparations, synthesis of shift reagents, and in vivo MR studies.

1. Jones, J. G., Cottam, G. L., Sherry, A. D., et al., Measurement of gluconeogenesis and pyruvate recycling in the rat liver: A simple analysis of glucose and glutamate isotopomers during metabolism of [1,2,3-$^{13}C_3$] propionate. *FEBS Letters* 412:131–137, 1997.
2. Seshan, V., Sherry, A. D., and Bansal, N., Evaluation of triple quantum-filtered ^{23}Na NMR spectroscopy in the in situ rat liver. *Magnetic Resonance in Medicine* 38:821–827, 1997.
3. Jeffrey, F. M., Storey, C. J., Sherry, A. D., et al., ^{13}C Isotopomer model for estimation of anaplerotic substrate oxidation via acetyl-CoA. *American Journal of Physiology* 271:E788–E799, 1996.
4. Radford, N. B., Fina, M., Benjamin, I. J., et al., Cardioprotective effects of hsp70 in transgenic mice. *Proceedings of the National Academy of Sciences USA* 93:2339–2342, 1996.

Mass Spectrometry



Bio-organic, Biomedical Mass Spectrometry Resource

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Research Emphasis

Mass spectrometric techniques for sequencing peptides and proteins as well as structural characterization of glycoconjugates and modified nucleic acids. Microsample handling and mass spectrometric analysis at the subpicomole level such as in identification of proteins separated by 2-D gel electrophoresis. Cotranslational and posttranslational modifications of proteins, including glycosylation, phosphorylation, acylation, etc., and xenobiotic modification such as that arising from mechanism-based enzyme inhibition and drug–protein adduct formation. Methodology includes liquid secondary ion and matrix-assisted lasers desorption ionization with high-energy collision-induced dissociation analysis and microbore HPLC-electrospray mass spectrometry.

Current Research

Structural biology; drug metabolites; high-resolution, liquid matrix-SIMS and electrospray and matrix-assisted laser desorption ionization for determination of biomolecular structure (i. e., carcinogens and drugs covalently bound to cellular macromolecules, polar drug conjugates, etc.); and structural studies of high molecular weight peptides, oligosaccharides, and heterobiopolymers.

Resource Capabilities

Instruments

PerSeptive Biosystems MALDI Voyager Elite and Voyager Elite STR DE reflectron TOF mass spectrometers, Mariner ES oaTOF mass spectrometers, Sciex API 300 ES triple quadrupole mass spectrometer, Kratos Concept 4-sector tandem mass spectrometer with fast scanning charged coupled device (CCD) array detector and VG 70S mass spectrometer.

Special Features

High-energy CID capability for de novo protein sequence determination and structural analysis. Capillary HPLC electrospray mass spectrometry and matrix-assisted laser desorption mass spectrometry with post-source decay for mass mapping and identification of 2-D gel spots. MS-FIT, MS-Tag and MS-Edman Web-accessible algorithms for gene and EST database interrogation with mass spectral data.

1. Caldera, P. S., Yu, Z., Knegtel, R. M. A., McPhee, F., Burlingame, A. L., Craik, C. S., Kuntz, I. D., and Ortiz de Montellano, P. R., Alkylation of a catalytic aspartate group of the SIV protease by an epoxide inhibitor. *Biorganic & Medicinal Chemistry* 5:2019–2027, 1997.
2. Sullivan, C. M., Matsui, N. M., Andrews, L. E., Clauser, K. R., Chapeaurouge, A., Burlingame, A. L., and Epstein, L. B., Identification of constitutive and G-interferon- and interleukin 4-regulated proteins in the human renal carcinoma cell line ACHN. *Cancer Research* 57:1137–1143, 1997.
3. Matsui, N. M., Smith, D. M., Clauser, K. R., Fichmann, J., Andrews, L. E., Sullivan, C. M., Burlingame, A. L., and Epstein, L. B., Immobilized pH gradient two-dimensional gel electrophoresis and mass spectrometric identification of cytokine-regulated proteins in ME-180 cervical carcinoma cells. *Electrophoresis* 18:409–417, 1997.
4. Medzihradszky, K. F., Besman, M. J., and Burlingame, A. L., Characterization of site-specific n-glycosylation of recombinant human factor VIII reversed phase high performance liquid chromatography-electrospray ionization mass spectrometry. *Analytical Chemistry* 69:3986–3994, 1997.

Mass Spectrometry Resource for Biology and Medicine

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Research Emphasis

High-sensitivity structural determinations and analyses of biological compounds. Emphasis on glycoconjugates, oligosaccharides, and proteins. Structure-activity studies related to immunology, carcinogenesis, developmental biology, parasitology and infectious diseases, tissue implantation and rejection. Biophysical properties of carbohydrates and glycoconjugates. Carbohydrate and amino acid sequence determinations of glycoproteins and proteins. Structure elucidation of unusual residues and posttranslational modifications. Characterization of oligonucleotides and metal complexes with biological relevance (e.g., imaging agents).

Current Research

Electrospray ionization and matrix-assisted laser desorption/ionization (MALDI) methods development for high-sensitivity (subpicomole) structural determinations relevant to glycobiology. Chromatographic and electrophoretic methods for analysis of complex mixtures. Derivatization and degradation protocols that may be carried out at low pmol levels with emphasis on maximizing the structural information in the mass spectra of the products. Ion chemistry studies to improve sensitivity and elucidate fragmentation patterns of native and derivatized biopolymers. MALDI-time of flight (TOF) approaches for surface analysis.

Resource Capabilities

Instruments

VG/Fisons Quattro II triple quadrupole tandem mass spectrometer with syringe pump and Hewlett Packard 1090 HPLC; electrospray ionization (ESI) and atmospheric pressure chemical ionization; capillary electrophoresis interface. Finnigan TSQ 700 triple quadrupole tandem mass spectrometer with syringe pump and ESI source. Triple quadrupoles may be operated in MS or MS/MS modes with skimmer-induced decomposition or low-energy collision-induced decomposition for sequence analysis. Finnigan MAT Vision 2000 MALDI reflectron TOF mass spectrometer with nitrogen (337 nm) ultraviolet laser and Er-YAG (2.94 µm) infrared laser operated in linear, reflectron, and post-source decay modes to yield molecular weight information and structural details.

Special Features

Guidance on sample preparation and data interpretation. By special arrangement: Microscale derivatizations, chemical and enzymatic degradations. Research on Fourier transform ion cyclotron resonance mass spectrometer with ESI and MALDI sources (added in 1998) will focus on sophisticated carbohydrate sequencing strategies.

1. Perreault, H., Hronowski, X. L., Koul, O., Street, J., McCluer, R. H., and Costello, C. E., High sensitivity mass spectral characterization of glycosphingolipids from bovine erythrocytes, mouse kidney and fetal calf brain. *International Journal of Mass Spectrometry and Ion Processes.* 169/170:351-370, 1997.
2. Jimenez, C. R., Li, K. W., Dreisewerd, K., Mansvelder, H. D., Brussaard, A. B., Reinhold, B. B., Van der Schors, R. C., Karas, M., Hillenkamp, F., Burbach, J. P. H., Costello, C. E., and Geraerts, W. P., M., Pattern changes of pituitary peptides in rat after salt-loading as detected by means of direct, semiquantitative mass spectrometric profiling. *Proceedings of the National Academy of Sciences USA* 94:9481–9486, 1997.
3. Branch-Moody, D., Reinhold, B. B., Guy, M. R., Beckman, E. M., Frederique, D. E., Furlong, S. T., Ye, S., Reinhold, V. N., Sieling, P. A., Modlin, R. L., Besra, G. S., and Porcelli, S. A., Structural requirements for glycolipid antigen recognition by CD1b-restricted T cells. *Science* 278:283–286, 1997.
4. Reinhold, V. N., Reinhold, B. B., and Costello, C. E., Carbohydrate molecular weight profiling, sequence, linkage, and branching data: ES-MS and CID. *Analytical Chemistry* 67:1772–1784, 1995.

Michigan State University Mass Spectrometry Facility

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Research Emphasis

The primary research focus is the development of new methodologies for obtaining structural information from proteins and peptides using matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Of particular interest are methods to characterize posttranslational modifications, such as phosphorylation and disulfide bond formation. Identifying sites of other covalent modifications, including those involved in protein cross-linking and active site localization with suicide inhibitors, is another area of interest. Two approaches are used in these studies: Direct sequencing of MALDI ionized peptides by MS/MS methods (e.g., post source decay); and molecular weight determinations of peptide mass mapping of proteins following enzymatic and/or chemical modification of the analyte. Methods are also under development to directly analyze proteins in two-dimensional electrophoretic gels or transfer membranes. Ancillary research areas include the characterization of lipids and carbohydrates by a variety of MS techniques, including MALDI-MS.

Resource Capabilities

The facility offers a variety of mass spectral techniques for users involved in diverse collaborative research projects and for service applications. Besides MALDI, other ionization methods available include fast atom bombardment (FAB), chemical ionization (CI), electron capture negative ionization, and electron ionization (EI). Electrospray ionization MS is also accessible on a restricted basis. High-resolution data (exact mass measurements) can be obtained under FAB, CI, or EI ionization modes. Five instruments are available for analyses to biomedical investigations.

1. Huang, Z. H., Wu, J., Roth, K. D. W., Yang, Y., Gage, D. A., and Watson, J. T., A picomole-scale method for charge derivatization of peptides for sequence analysis by mass spectrometry. *Analytical Chemistry* 69:137–144, 1997.
2. Kang, S., Liao, P. C., Gage, D. A., and Esselman, W. J., Identification of in vivo phosphorylation sites of CD45 protein-tyrosine phosphatase in 70Z/3.12 cells. *Journal of Biological Chemistry* 272:11588–11596, 1997.
3. Wu, J., and Watson, J. T., A novel methodology for assignment of disulfide bond pairings in proteins. *Protein Science* 6:391–398, 1997.
4. Zaluzec, E. J., Gage, D. A., and Watson, J. T., Matrix-assisted laser desorption ionization mass spectrometry: Applications in peptide and protein characterization. *Protein Expression and Purification* 6:109–123, 1995.

National Resource for Mass Spectrometric Analysis of Biological Macromolecules

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Research Emphasis

Development of mass spectrometric instrumentation and methods for solving challenging biological problems rapidly. Rapid, accurate mass spectrometric measurement of peptides and proteins and in developing hardware tools, software tools, and new methodologies useful to biomedical researchers.

Current Research

Development of matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization mass spectrometric instrumentation; time-of-flight mass spectrometry; and ion trap mass spectrometry. Investigations of the MALDI and electrospray ionization processes and the gas-phase fragmentation of biopolymers. Probing the interaction between biomolecules. Rapid, sensitive identification of proteins. Elucidation of posttranslational modifications. Development of the mass spectrometer as a tool for the protein x-ray crystallographer and NMR spectroscopist. Development of mass spectrometry as a tool for the biologist. Development of Web-based bioinformatics software and associated software tools for investigating proteins using mass spectrometry.

Resource Capabilities

Instruments

In-house–constructed UV-MALDI delayed-extraction linear time-of-flight mass spectrometer for very high sensitivity measurements of peptides and proteins; commercial (PerSeptive Biosystems STR) MALDI-delayed extraction reflectron time-of-flight mass spectrometer for high-accuracy measurements; in-house–constructed IR/UV-MALDI delayed-extraction linear time-of-flight mass spectrometer for basic research investigations; commercial (Finnigan-MAT TSQ-700) triple quadrupole electrospray ionization mass spectrometer for MS, MS-MS (i.e., tandem mass spectrometry), LCMS, and LCMS-MS measurements; in-house–constructed UV-MALDI ion trap mass spectrometer for the rapid, sensitive MS and MS-MS of peptides; commercial (Finnigan-MAT LCQ) electrospray ionization ion trap mass spectrometer for LCMS-MS and infusion MS-MS of peptides.

Software

Publicly accessible mass spectrometry computer program/database with a set of useful software tools (e.g., for protein identification, spectrum manipulation, disulfide mapping, etc.) that can automatically access all current information concerning any given protein or open reading frame. Available at URL http://PROWL.rockefeller.edu.

Special Features

The combination of instruments allows for the rapid identification of proteins, the elucidation of posttranslational modification, the determination of compactly folded protein domains, and the determination of interactions between proteins.

1. Qin, J. and Chait, B. T., Rapid, accurate identification and characterization of posttranslational modifications of proteins by MALDI ion trap mass spectrometry. *Analytical Chemistry* 69:4002–4009, 1997.
2. Fenyo, D., Zhang, W., Chait, B. T., and Beavis, R. C., Internet-based analytical chemistry resources: A model project. *Analytical Chemistry* 68:721A–726A, 1996.
3. Beavis, R. C. and Chait, B. T., Matrix-assisted laser desorption mass spectrometry of proteins. *Methods in Enzymology* 270: 519–551, 1996.
4. Cohen, S. L., Domain elucidation by mass spectrometry. *Structure* 4:1013–1016, 1996.

Resource for Biomedical and Bio-organic Mass Spectrometry

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Resource Emphasis

To provide access to state-of-the-art mass spectrometric instrumentation for researchers through service and collaborative research arrangements; to maintain a broad range of mass spectrometric instrumentation well-suited to studies of biomolecules; and to educate students in the mass spectrometric arts. A unique characteristic of this resource is that it has facilities in both the chemistry department and the medical school of Washington University, with an interactive staff.

Current Research

Instrument and method development in tandem sector, time-of-flight, and Fourier transform mass spectrometry are aims at the Chemistry site. Peptides, proteins, carcinogen-modified DNA fragments, and lipids are the foci. Stable isotope tracer studies and the investigation of complex lipids are aims at the Medical School site. Specific applications are the metabolism of glucose and fatty acids, and the role of lipids in the biochemistry of insulin-producing cells.

Resource Capabilities

A variety of instrumentation based on different analyzers and a range of state-of-the-art ionization techniques well-suited to biological applications. All equipment is supported by computer hardware and software resources.

Instruments

At the Chemistry Department site: Micromass ZAB-T 4-sector tandem magnetic sector mass spectrometer (BEBE) with array detection capability, Kratos MS-50 3-sector tandem magnetic sector mass spectrometer (EBE), and VG ZAB-SE double-focusing magnetic sector mass spectrometer (BE). These instruments are equipped with most ionization methods including electrospray (ESI). Nonsector instruments include: PerSeptive Voyager RP time-of-flight mass spectrometer with matrix-assisted laser desorption ionization (MALDI), reflectron, delayed-extraction, post source decay, and collision-cell capability, Finnigan LCQ ion-trap mass spectrometer with HPLC inlet and ESI, Finnigan T-30 Fourier transform mass spectrometer with 3 tesla magnet, and two custom-built Fourier transform mass spectrometers.

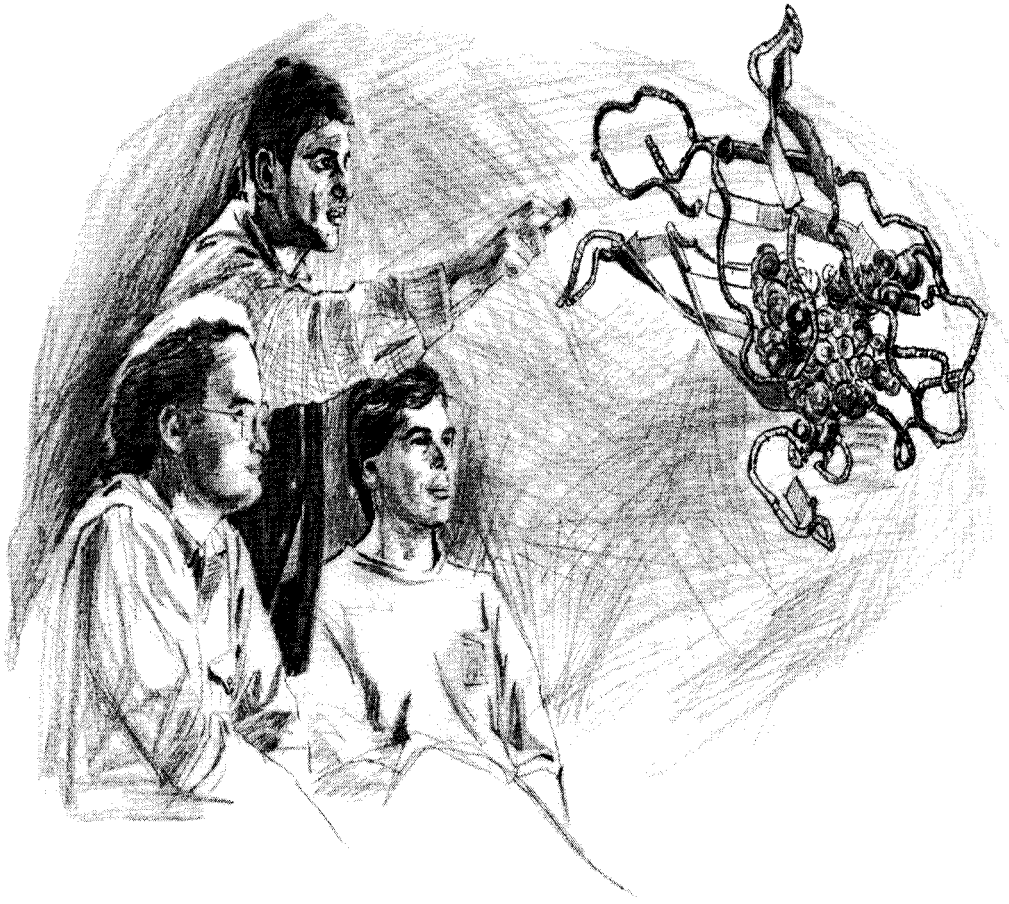
Equipment available at the Medical School site: Finnigan TSQ 7000 triple quadrupole with ESI, Finnigan SSQ 7000 single quadrupole gas chromatograph/mass spectrometer, two Finnigan 3300 quadrupole mass spectrometers dedicated to positive chemical ionization (CI), three Hewlett Packard 5988 mass spectrometers with negative/positive CI, three Hewlett Packard 5970 EI mass spectrometers, and a VG SIRA Series II isotope ratio mass spectrometer with Isochrom on line-combustion apparatus.

Special Features

The four-sector ZAB-T instrument is one of two in the United States and is the only one available to academic biomedical researchers. This instrument and the quadrupole and ion-trap instruments permit the facile investigation of collision-induced dissociation processes at both high and low energies. The isotope tracer facility at the Medical School specializes in the application of this technology in metabolism studies.

1. Nelson, C. A., Vidavsky, I., Viner, N. J., Gross, M. L., Unanue, E. R., Amino-terminal trimming of peptides for presentation on major histocompatibility complex class II molecules. *Proceedings of the National Academy of Sciences USA* 94:628–633, 1997.
2. Rogan, E., Gross, M. L., et al., Molecular origin of cancer: Catechol estrogen-3,4-quinones as endogenous tumor initiators. *Proceedings of the National Academy of Sciences USA* 94:10937–10942, 1997.
3. Nemirosvskiy, O. V., Ramanathan, R., and Gross, M. L., Investigation of calcium-induced, noncovalent association of calmodulin with melittin by electrospray ionization mass spectrometry. *Journal of the American Society of Mass Spectrometry* 8:809–812, 1997.

Optical and Electron Microscopy



Biological Microscopy & Image Reconstruction Resource

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Research Emphasis

Computer-enhanced 3-D light and electron microscopic methodologies for the study of high-resolution structure/function relationships in tissues, cells, and macromolecular assemblies.

Current Research

Development of thick-section–based high- and intermediate-voltage electron microscopic (EM) tomography of cells and organelles in situ and in vitro. 3-D imaging of frozen-hydrated sections and macromolecules. Laser-based light microscopic (LM) microsurgery and micromanipulation studies of organelles in living cells. 3-D EM reconstructions of the structure underlying events followed in the living cell up to the point of fixation. 3-D structure, function, and interaction of cell organelles including centrosomes, kinetochores, chromosomes, mitochondria, endoplasmic reticulum, golgi, and cytoskeletal elements. Structure and function of macromolecular complexes including ribosomes, nuclear pore complexes, triad-junctions, mitochondrial membrane channels. Tomographic studies on the mineralization of collagen during bone formation and the interaction of dental prosthetics with oral tissues.

Resource Capabilities

Instruments

AEI EM7 MKII HVEM (100–1,200 KeV) can image whole-cell mounts or selectively stained sections >5 µm thick. A JEOL JEM-4000FX IVEM(100–4,000 KeV) with a LaB_6 cathode, a STEM attachment, a 5-axis computer-controlled goniometer, and a Gatan cryotransfer stage. A Zeiss EM 910 electron microscope (120 KeV). A Balzers HP-10 high-pressure freezer and a Balzers FSU 010 freeze substitution unit. A de Senarmont differential interference contrast-based laser microsurgery/optical-trapping video-enhanced LM workstation (based on Q-switched, pulsed Nd:YAG Surelite II and continuous wave Nd:YAG 116 EF-CW-3 Quantronix lasers). A Cell Robotics Laser-tweezers system. A Bio-Rad Laser Scanning Confocal System mounted on an Olympus IMT-2 LM with argon-ion and HeNe lasers for exciting a large range of fluorochromes. Nikon Quad-Fluor optics and a Photometrics PXL CCD camera. A Perkin Elmer PDS-1010A flatbed microdensitometer and a Dage/MTI model 81 video camera (with an Androx ICS-400 image processing board in a SUN workstation). 4-processor Silicon Graphics (SG7) SGI R8000 ONYX Reality Engine II, connected to 11 SGI Indigo^2 and Indy workstations.

Special Features

The HVEM is equipped with a single tilt (+/–70°) and tilt-(+/–60°) rotation (360°) stages. A video system can be used for low-dose imaging and for screening beam-sensitive specimens. The IVEM is equipped with the Tietz system for the automated collection of tomographic data sets. The Zeiss 910 is equipped with a 1024 x 1024 Gatan slow-scan CCD imaging system, a LaB_6 cathode and an Oxford cryotransfer unit for imaging frozen-hydrated specimens. The video-enhanced light microscopes can be coupled to Paultek P100 CCD chip or various DAGE video cameras, PC or SUN Sparc station-based Image 1 or ISEE image processing systems, and optical memory disk recorders. ANALYZE software on an IBM RISC 6000 graphics workstation. SPIDER and WEB. Sterecon. O, AVS, EXPLORER, and VOXELVIEW.

1. Khodjakov, A., Cole, R. W., et al., Chromosome fragments possessing only one kinetochore can congress to the spindle equator in PtK1 cells. *Journal of Cell Biology* 136:229–241, 1997.
2. Mannella, C. A., Marko, M., et al., Reconsidering mitochondrial structure: New views of an old organelle. *Trends in Biochemical Science* 22:37–38, 1997.
3. Khodjakov, A. and Rieder, C. L., Kinetochores moving away from their associated pole do not exert a significant pushing force on the chromosome. *Journal of Cell Biology* 135:315–328, 1996.

Integrated Microscopy Resource

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Research Emphasis

Studying the structure and dynamics of the cytoskeleton. Live cells and tissues observed using confocal imaging, low-dose, two-photon fluorescence imaging, and Nomarski bright-field imaging. Multifocal plane time-lapse (i.e., 4-dimensional) datasets of cellular or tissue dynamics may be recorded. At selected time-points, specimens may be rapidly immobilized by high-pressure freezing and prepared for electron microscopy. Live-specimen imaging and specimen preparation techniques. Nuclear pore complex, cytoskeleton dynamics in developing embryos, contractile ring formation in dividing cells, and mechanisms of muscle assembly.

Current Research

Optical workstations to image and optically manipulate live specimens. Two-photon excitation imaging, infrared Nomarski imaging, and 4-D image archiving. Specimen preparation techniques for electron microscopy using the high-pressure freezer for rapidly immobilizing and preserving structure and antigenicity to facilitate immunolabeling.

Resource Capabilities

Optical sectioning technique of two-photon excitation minimizes phototoxicity when visualizing fluorescent probes in live material, with much better localization for uncaging experiments. High-pressure freezing allows comparatively large specimens to be rapidly cryo-immobilized without ice-crystal damage. Specimens can be low-temperature embedded without fixation to preserve antigenicity, or embedded at room temperature and fixed in frozen state for the highest degree of structural preservation.

The high-performance FESEM features high-resolution (0.8 nm at 30 KeV) with the capacity to achieve good resolution at low voltages (5 nm at 1 KeV). This allows detailed surface features to be examined with minimal specimen damage; the high resolution available at high voltages allows detail to be resolved on structures such as viruses that can only be obtained by averaging techniques in a TEM. A backscattered electron detector facilitates detection of immunogold labeling on specimens.

Instrumentation

Optical. Two-photon imaging system using a new all solid-state diode laser operating at a wavelength of 1047 nm (doubles to 523 nm by two-photon absorption within the specimen) based on a Bio-Rad MRC 600 confocal microscope interfaced to a Nikon Diaphot 300 inverted microscope, with a piezo-drive micromanipulator for intracellular injections. Multifocal plane time-lapse (4-D) system with Nomarski optics for recording intracellular and tissue dynamics. A Bio-Rad MRC 600 confocal microscope on a Nikon Optiphot microscope with an Argon/Krypton laser.

Electron microscopes. Hitachi S-900 FESEM equipped with an in-lens specimen chamber, a field emission electron gun, a high-sensitivity backscattered electron capture system with a resolution of up to 200 X 2000 pixels.

Sample preparation. Bal-Tek HPF-010 high-pressure freezer that rapidly freezes specimens at a pressure of around 2,000 bar to prevent ice crystal formation. Bal-Tek Med-010 planar magnetron sputter coater with a cryo specimen holder; a critical point dryer; other vacuum coating equipment; Bal-Tek FSU-010 freeze substitution unit; Balzers BAF-400 freeze fracture machine.

1. Wokosin, D. L., Centonze, V. E., Crittenden, S., and White, J., Three-photon-excitation fluorescence imaging of biological specimens using an all-solid-state laser. *Bioimaging* 4:208–214, 1997.
2. Chen, Y., Zardi, L., and Peters, D. M. P., High-resolution cryo-scanning electron microscopy study of macromolecular structure of fibronectin fibrils. *Scanning* 19:349–355, 1997.
3. Ris, H., High-resolution field-emission scanning electron microscopy of nuclear pore complex. *Scanning* 19:368–375, 1997.
4. Thomas, C. P. D., Hardin, J., and White, J., Four-dimensional imaging: Computer visualization of 3-D movements in living specimens. *Science* 273:603–607, 1996.

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Research Emphasis

Development of technologies for deriving and visualizing the fine 3-D structure of cellular processes and subcellular organelles at electron microscopic resolution, using a 400 KeV intermediate-voltage transmission electron microscope (IVEM) to obtain structurally rich images from specimens several microns thick, especially when they have been stained selectively. Model biological problems that clearly benefit from the IVEM. Computer-aided techniques for deriving the 3-D information contained within these sections, including tomographic reconstruction and analysis of stereopairs, with emphasis on obtaining correlated 3-D light and electron microscopic information on the same specimen using confocal microscope and IVEM. Placing the IVEM online so researchers can access this unique instrument via remote workstations.

Current Research

Efforts are driven by a range of biological issues in cell and molecular biology, with particular emphasis on neurobiology. Specimen preparation focuses on development of new and better techniques for selective staining of cells and tissues to facilitate acquisition of 3-D data using the IVEM. Traditional heavy metal and enzyme cytochemical techniques, and 3-D labeling of proteins and nucleic acids within cells and tissues using immunolabeling, in situ hybridization, and nonimmunological cellular probes such as toxins or tagging of proteins using molecular biological techniques. Several novel strategies for efficient photooxidation of fluorescent dyes render the same preparation suitable for correlated confocal and IVEM analysis, and tremendously expand the repertoire of selective stains available to biologists. Active development of computer-aided methods to enhance image contrast and extract accurate 3-D information from within single thick sections or series of sections. Methods for deriving 3-D structure from series of tilt images using electron tomography to obtain quantitative structural information on specimens, including spiny dendrites, synaptic structures, and mitochondria. Improved speed and fidelity of reconstruction methods achieved via new reconstruction algorithms on parallel machines at the San Diego Supercomputer Center. Streamlining the tomographic procedure by automating acquisition of tilt images. Remote acquisition of images and tilt series by off-site researchers for a small number of test sites. Semi-automated image acquisition for serial section and tomographic methods of reconstruction using conventional and high-performance computers.

Resource Capabilities

Instruments

400 KeV electron microscope, JEOL model JEM4000 EX/SEG. Usable voltage range, 100–400 KeV; magnification range, 150-250,000 x; resolution better than 2.5 Å point to point; five grid specimen holder; grid diameter of 3 mm; goniostage tilting range typically 120°, 360° with special specimen holder; unique high-contrast imaging mode; GATAN video rate camera for online observation; GATAN cryostage cooled by liquid nitrogen; dark field by tilted beam and rotary hollow cone; film size 3.25 x 4 in; 14-bit 1K x 1K Photometrics cooled CCD camera lens coupled to the microscope for digital image acquisition. Confocal microscopes. Biorad MRC 1024 and a video rate Nikon RCM 8000 three-channel laser scanning confocal microscopes.

Software

MRC and Suprim packages. Synu and Ducky systems. Programs for tilt image alignment. ANALYZE.

1. Perkins, G., Renkin, C., Martone, M., Young, S., Ellisman, M., and Frey, T., Electron tomography of mitochondria: Membrane contacts. *Journal of Structural Biology* 119:260–272, 1997.
2. Hessler, D., Young, S. J., and Ellisman, M. H., A flexible environment for the visualization of 3-D biological structures. *Journal of Structural Biology* 116:113–119, 1996.
3. Martone, M. E., Pollock, J. A., Jones, Y. Z., and Ellisman, M. H., Ultrastructural localization of dendritic messenger RNA in adult rat hippocampus. *Journal of Neuroscience* 16:7437–7446, 1996.

STEM Mass Mapping & Heavy Atom Labeling of Biomolecules

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Research Emphasis

The Scanning Transmission Electron Microscope (STEM) produces an image one point at a time by moving a finely focused electron beam over a specimen. The numbers of scattered and unscattered electrons are measured at each point, giving a quantitative determination of the scattering power of the irradiated volume. For thin specimens (single biological molecules or complexes), this gives a direct measure of local mass; summing over an entire object gives its total mass. The spatial resolution of this mass map is typically 2–4 nm, limited by radiation damage to the freeze-dried specimen (probe size is only 0.25 nm). The contrast is high enough to "see" unstained DNA, proteins larger than 10 KDa, lipid layers, and single heavy atoms.

Most STEM studies use this quantitative imaging capability to determine the number and spatial arrangement of subunits (of known size) in a larger structure. Typically 50 projects are active at any given time: assembly of virus particles (5 projects), Alzheimer's filaments (2), prion filaments (1), neurofilaments (1), fibrin clots (1), DNA/protein complexes (5), earthworm hemoglobin (1). A wide variety of intermediates can be recognized and characterized in a single preparation. Intact structures from various sources can be compared in parallel preparations. Purified subcellular components in the size range 30 KDa–100 MDa are the subject of many more studies. Tobacco mosaic virus is included in all STEM specimens as a control for specimen preparation quality, radiation damage and mass calibration. Mass accuracy ranges from 10% for small particles to better than 1% for objects larger than 1 MDa.

In structures with cylindrical or spherical symmetry, the projected mass distribution (the direct STEM output) can be transformed to give a radial density profile. This usually requires aligning and averaging images of many similar particles in order to reduce noise.

Specific labeling of interesting sites within complexes provides additional information about orientation of subunits or location of one type of unit in a mixed complex. Heavy atom clusters containing 11 or 67 gold atoms in a dense core provide adequate signal for low-dose visualization. These have been developed as monofunctional reagents that can be attached directly to a structure (e.g., accessible sulfhydryl or amino side chain in a protein) or through an intermediary such as an antibody fragment, biotin/avidin or histidine tag. Localization is 2–4 nm, limited by radiation damage to the freeze-dried specimen. Higher spatial resolution can be obtained using the low-density negative stain methylamine vanadate to embed the specimen. Unlike typical negative stains, this does not obscure the gold cluster specific labels.

Resource Capabilities

Instruments

STEM1 custom built with 40 KeV cold field emission gun (FEG), high-field immersion objective (Cs=1 mm) remote UHV freeze dry system, vacuum transfer of frozen or freeze-dried specimens, cold specimen stage (–150° C), efficient dark field annular detectors, digital control/data acquisition/display, data distribution by Internet or optical disk. STEM3, similar with improved performance and electron energy loss spectrometer (EELS) for elemental mapping. UHV carbon evaporator and UHV freeze dryer for specimen prep. Display and mass measurement on PC.

1. Wall, J. S., Hainfeld, J. F., and Simon, M. N., Scanning transmission electron microscopy (STEM) of nuclear structures. In *Methods in Cell Biology* (Berrios, M., ed.), pp. 139–166. New York: Academic Press, 1998 .
2. Citowsky, V., Guralnick, B., Simon, M. N., and Wall, J. S., The molecular structure of agrobacterium VirE2-single stranded DNA complexes involved in nuclear import. *Journal of Molecular Biology* 271:718–727, 1997.
3. Gregori, L., Hainfield, J. F., Simon, M. N., and Goldgaber, D., Binding of amyloid beta protein to the 20 S proteasome. *Journal of Biological Chemistry* 272:58–62, 1997.
4. Linderoth, N. A., Simon, M. N., and Russel, M., The filamentous phage pIV multimer visualized by STEM. *Science* 278:1635–1638, 1997.

Three-Dimensional Electron Microscopy of Macromolecules

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Research Emphasis

This resource specializes in development of the technology of electron imaging and the diffraction of biological macromolecular assemblies toward atomic resolution. Active collaborative projects include 3-D reconstruction of images of cytoskeletal protein assemblies, viruses, protein-nucleic acid complexes, and membrane channel proteins. These structures are particularly difficult to study by x-ray crystallography and NMR.

Current Research

Develop methodology for electron crystallography of macromolecules at atomic resolution; build high-resolution cryoholders; implement spot scan and CCD camera data capture; implement computer automation of electron microscope alignment and data collection; write appropriate software for interactive, automated image processing; apply electron cryomicroscopy techniques to visualize structures of macromolecular assemblies and subcellular components at different functional states; develop procedures for preparing highly ordered 2-D arrays of macromolecules.

Resource Capabilities

Instruments

JEOL 4000 electron microscope with a slow scan, 1,024 x 1,024 CCD camera; JEOL 1200 electron microscope; cryo-specimen preparative apparatus; high-resolution Gatan cryospecimen holders; Perkin-Elmer microdensitometer 1010 M; Eikonix CCD scanner, Zeiss PHODIS SC scanner, Silicon Graphics workstations.

Other Computing Facilities

Silicon Graphics ONYX2 supercomputer is available through the Biomedical Computation and Visualization Laboratory at Baylor College of Medicine (URL: http://www.bcm.tmc.edu/bcvl/).

1. Chiu, W. and Schmid, M. F., Pushing back the limits of electron cryomicroscopy. *Nature Structural Biology* 4:331–333, 1997.
2. Thuman-Commike, P. A. and Chiu, W., Improved common-line based icosahedral virus particle image orientation estimation algorithms. *Ultramicroscopy* 68:231–256, 1997.
3. Avila-Sakar, A. J. and Chiu, W., Visualization of beta sheets and side chain clusters in 2-dimensional periodic arrays of streptavidin on phospholipid monolayers by electron crystallography. *Biophysical Journal* 70:57–68, 1996.
4. Schmid, M. F., Jakana, J., Chiu, W., and Matsudaira, P., A 7 Å projection map of frozen, hydrated acrosomal bundle from *Limulus* sperm. *Journal of Structural Biology* 115:209–213, 1995.

Three-Dimensional Fine Structure of Cells and Tissues

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Research Emphasis

High-voltage electron microscopy offers biologists the possibility of viewing the fine structure of specimens with thicknesses that defy imaging by other forms of EM. Relevant samples include whole cultured cells, isolated organelles such as chromosomes, macromolecular assemblies such as the mitotic apparatus, and thick sections of cells or tissues. A cold stage permits microscopy while specimens are frozen and hydrated with vitreous ice.

Stereo images can be taken to facilitate 3-D viewing, but for more detailed 3-D information, multiple tilted views can be assembled off-line to form a tomogram. Three-dimensional reconstructions with good resolution (~10 nm) can be obtained with specimens up to a micrometer thick by using large numbers of serial tilts and reconstruction by computer. This facility is also developing technology for the specific labeling of macromolecular components of cells, using immunocytochemistry or the photoconversion of fluorescently tagged macromolecules. A video system is available to aid operators and facilitate viewing of faint biological material; a cooled CCD camera is about to be installed. The Resource's computer facilities permit both 3-D reconstruction and modeling of serial thin or thick sections.

Resource Capabilities

Instruments

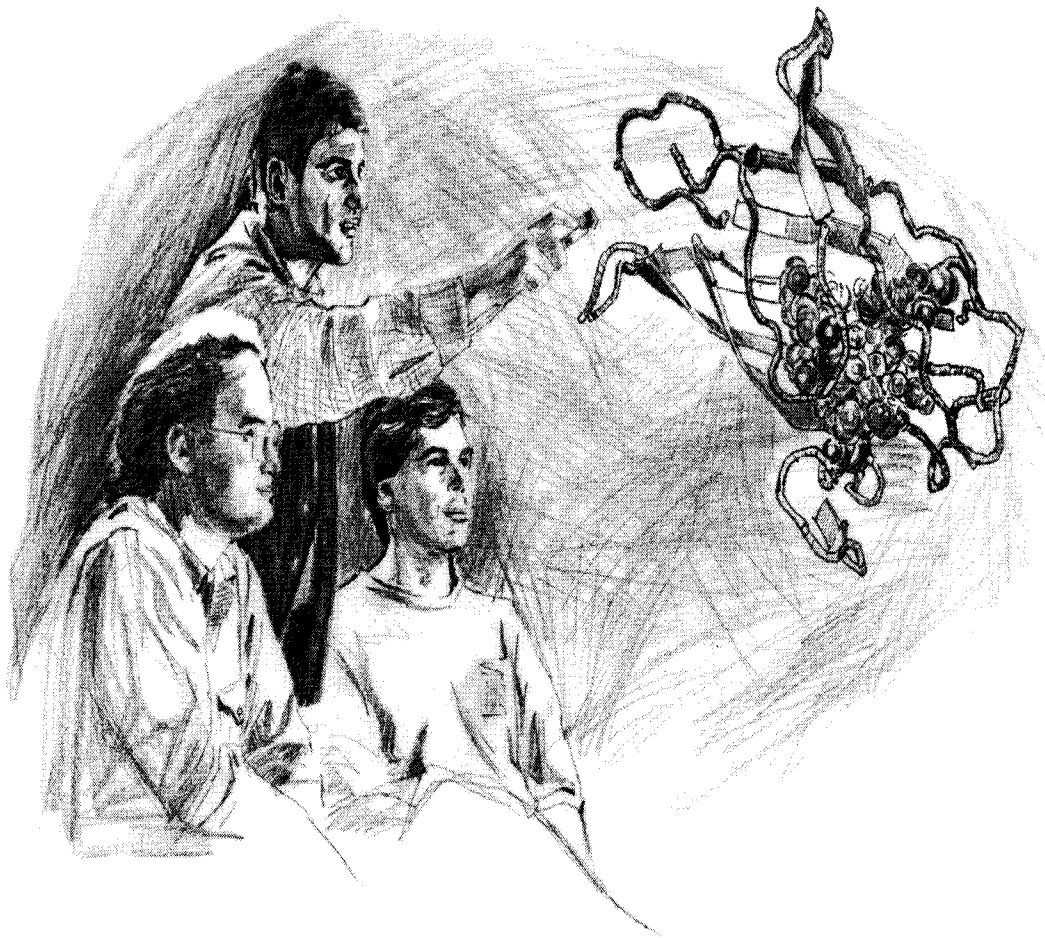
One MeV electron microscope (JEM 1000) and support equipment for specimen preparation. Image processing computers: SGI Indigo XZ4000, Indy R4600, O2R5000, and Octane SSI Dual R10,000.

Special Features

Usable voltage range 500 KeV to 1 MeV; side entry operation, grid diameter of 3 mm; magnification range, 150–250,000 x; resolution better than 3 Å lattice; routine goniostage tilting range ±60° about any axis; dark field by tilted beam; electron diffraction camera lengths 1–4 m, film size 3 x 4"; cryostage cooled by liquid nitrogen operational for viewing specimens from 110 K to room temperature; image processing software for 3-D reconstruction from serial tilts or serial sections.

1. Mastronarde, D. N., Dual-axis tomography. *Journal of Structural Biology* 120:343–352, 1997.
2. Kremer, J. R., Mastronarde, D. N., and McIntosh, J. R., Computer visualization of three-dimensional image data using IMOD. *Journal of Structural Biology* 116:71–76, 1996.
3. Winey, M., Mamay, C. L., O'Toole, E. T., Mastronarde, D. N., Giddings, T. H., McDonald, K. L., and McIntosh, J. R., Three-dimensional ultrastructural analysis of the *Saccharomyces cerevisiae* mitotic spindle. *Journal of Cell Biology* 129:1601–1615, 1995.

Simulation and Computation



Human Genetic Analysis Resource

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Research Emphasis

Developing a user-friendly software package, S.A.G.E., that may be used to analyze family data to determine if the variability of a trait, either quantitative or qualitative, is significantly due to Mendelian segregation at a single genetic locus; if there is association between a quantitative trait and a known polymorphic genetic marker; if there are genetic loci linked to a known genetic marker that underlie variability in a trait; and to determine the order of a set of genetic marker loci along a chromosome.

Current Research

Theoretical development of statistical methods for the analysis of family data, especially to detect and identify genetic components that underlie disease susceptibility. Incorporating these methods into appropriate computer programs and making the programs generally available to other human geneticists in a well-documented and user-friendly form. Testing the validity, power, and robustness of the statistical procedures, especially to differentiate genetic causes from alternative environmental causes for familial aggregation. Application of methods and programs in collaborative projects to identify single genes that play roles in the etiology of various diseases.

Resource Capabilities

Hardware

High-end Pentium PC systems running Microsoft Windows 95 and Windows NT. Larger scale computing is done with 7 DEC Alpha AXP workstations and several Sun Microsystems workstations. Centralized network and computation services are provided by two DEC Alpha Servers each with 64 megabytes of memory and a total of 8 gigabytes of online storage. Network and Internetwork access is through a 10Base-T Ethernet with a T1 gateway to a regional Internet provider. Media support includes 4 mm and 8 mm tape, 9 track tape, QIC cartridge, CD-ROM, and floppy disk. A color printer, a color scanner, and large capacity laser printers.

Software

Primary operating systems are Digital Unix (OSF/1), Microsoft Windows (NT and 95), Solaris (SunOS) and Linux. Mathematical and statistical packages include SAS and Mathematica. Development software includes Fortran 77, C, C++, Perl, Java, and Tcl/Tk. The S.A.G.E. package that performs statistical analysis for genetic epidemiology is continually being developed and used for data analysis and simulation studies. It is written in ANSI Fortran-77, and has been translated to C; a graphical user interface is being added and the programs rewritten in C++.

Interactive Graphics for Molecular Studies and Microscopy

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Research Emphasis

Computer graphics software and hardware platforms that enable the user to study biologically significant molecules. Nanomanipulator systems that combine scanning probe microscopy with virtual reality technology that, in effect, place the operator on the surface of the material being studied, in control of the microscope tip. Facilities and software are available to qualified users, and software packages that have reached a stage suitable for dissemination are available via Internet.

Resource Capabilities

Software

DOCKER is a system for studying interactions between two molecules. One molecule is treated as a rigid structure. The user controls the position, orientation, and rotatable bonds of the other structure. The binding energy, force, and torques between the molecules are calculated in real time and displayed to the user's view and feel.

SCULPT is a system developed in-house, now offered by Interactive Simulations, Inc..

VIEW is a system for generating impromptu visualizations of molecular structures. The user chooses graphic elements to generate representations of any aspect of the geometry. Software tools speed the construction of the graphic representations, and the user can define new tools for specific purposes.

NANOSCAPE is a virtual-reality interface for controlling an atomic force microscope and for observing its output as a 3-D image in real time. The user can change the viewpoint, "feel" the contours of the surface, and control the microscope as it modifies the surface.

CORWIN is a real-time density map fitting system with displays of both real space and reciprocal space.

PIT is an implementation of Richardson's MAGE system using a wall-size display with tracking of two heads.

Hardware

Master input stations for natural, direct manipulation of computer-simulated structures with force display: A six-axis electromanipulator arm, and a four-axis PHANToM. SGI Reality Engine, Reality Engine 2, hardware developed in-house for rendering complex pictures in real time. Several head-mounted display and tracking devices.

1. Falvo, M. R., Clary, G. J., Taylor, R. M., II, Chi, V., Brooks, F. P., Jr., Washburn, S., and Superfine, R., Bending and buckling of carbon nanotubes under large strain. *Nature* 389:582–584, 1997.
2. Falvo, M., Superfine, R., Washburn, S., Finch, M., Taylor, R. M., Chi, V. L., and Brooks, F. P., The nanomanipulator: A teleoperator for manipulating materials at the nanometer scale. *Proceedings of the International Symposium on the Science and Technology of Atomically Engineered Materials.* (Richmond, VA, October 1995). Singapore: World Scientific Publishers.
3. Finch, M., Chi, V., Taylor, R. M., Falvo, M., Washburn, S., and Superfine, R., Surface modification tools in a virtual environment interface to a scanning probe microscope. *Proceedings of the ACM Symposium on Interactive 3-D Graphics* (Monterey, CA, April 9–12, 1995). Computer Graphics, ACM SIGGRAPH, 13–18, 1995.
4. Varshney, A., Brooks, F. P., Jr., Richardson, D. C., Wright, W. V., and Manocha, D., Defining, computing, and visualizing molecular interfaces. *Proceedings: Visualization '95* (Atlanta, October 1995). Los Alamitos, CA: IEEE Computer Society, 36–43, 1995.

Multiscale Modeling Tools for Structural Biology

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Research Emphasis

Problems in structural biology increasingly require researchers to move between models of low-resolution and detailed atomic models to fully explore and exploit experimental information. This resource focuses on development of new and integrated approaches to multiscale modeling with an emphasis on modeling large-scale assemblies of nucleic acids and proteins with nucleic acids; developing methods that combine lattice-based dynamic Monte Carlo and all atom molecular dynamics; studying physical processes and the development of models for the interactions associated with virus assembly; tying these research threads together through the development and distribution of computer codes to make such multiscale simulations and modeling readily accessible to the scientific community at large.

Current Research

One initial research effort focuses on development of models for RNA and tools that permit facile construction of such models from low-resolution information. Related work on proteins emphasizes the facile and robust construction of models of protein structures at atomic resolution from lattice-based folding algorithms. These methods and models are being used to explore alternative folding pathways for protein molecules. Virus assembly has also been an initial focus. This resource has developed a methodology to classify virus particles based on an inventory of their interfacial interactions. Software has been developed and tested for the exploration of assembly pathways and the role of individual interfacial side chains in modulating interface formation. Developments and research progress in all focus areas are advancing rapidly. To keep the scientific community abreast of ongoing developments, there is an up-to-date report of efforts on the Web page, with online services associated with software applications, documentation, and test cases. Interested scientists should look for these announcements and services at the URL given above.

Resource Capabilities

Hardware and Software

This resource is equipped with a high-performance dual-processor Silicon Graphics Octane graphics server, a four-processor Silicon Graphics Origin200 compute server, and an O2 webserver workstation. In addition to these dedicated high-performance computational resources, large-scale modeling and simulation studies are performed on TSRI servers, including four 12-processor Silicon Graphics R10000 servers and an 80-processor Cray T3E supercomputer.

Software under development includes lattice-based Monte Carlo sampling codes, NAB (a software package to rapidly construct nucleic acid structures at atomic resolution), yammp (a molecular mechanics and modeling code directed toward low-resolution modeling of RNA and DNA), and modules for the widely distributed software packages CHARMM and AMBER. Information about use and distribution of this software is available at the Web site.

1. Reddy, V., Giesing, H., Morton, R., Kumar, A., Post, C., Brooks, C. L., III, and Johnson, J., Energetics of quasi-equivalence: Computational analysis of protein–protein interactions in icosohedral viruses. *Biophysics Journal* 74:546–558, 1998.

National Biomedical Computation Resource

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Research Emphasis

The National Biomedical Computation Resource is a collaboration of the San Diego Supercomputer Center (SDSC) at the University of California, San Diego; the Scripps Research Institute; the University of California, San Francisco; and Molecular Simulations, Inc. Its primary goal is to enhance the usefulness of high-performance computing and visualization in biomedical fields. This goal has three main components: To accelerate the movement of widely used biomedical applications onto modern scalable parallel computer architectures, to perform basic research in biomedicine ranging from atomic to organismic levels, and to train a cadre of researchers with experience in both parallel computing and biomedical research. Core research projects have been carefully chosen to cover the sizes of interest to biomedical research and to represent problems widespread in biomedicine, so experience from core research projects will be useful to other projects.

Current Research

Integration of solvent modeling with density functional theory quantum mechanical calculations, and the application of these methods to biological molecules. Efficient parallel implementations of the AMBER molecular modeling package for calculating minimum energy structures and molecular dynamics simulations of macromolecules. The parallelization of tomographic methods used to reconstruct 3-D images. Methods for pattern recognition in protein and nucleic acid sequences, and their extension to protein and nucleic acid structures. Integration of high-performance computing and visualization in the study of macromolecules, with an emphasis on molecular docking as a model system. Collaborative projects: Integration of quantum mechanical and molecular dynamic approaches to the study of hemoglobin; finite-element modeling of cardiac electromechanics; parallelization of RNA secondary structure prediction methods.

Resource Capabilities

Instruments

A 256-node CRAY T3E parallel supercomputer. Each processing element is a DEC Alpha 21164 running at 300 MHz with 128 megabytes of memory, for a peak performance of 154 GFLOPS and 32 gigabytes of total memory.

128-node IBM RS/6000 SP parallel supercomputer. Each processing element runs at 160 MHz with 256 megabytes of memory, for a peak performance of 82 GFLOPS and 32 gigabytes of total memory.

Biocelerator system (Compugen, Ltd.). An FPGA-based dedicated computer system that compares sequences and sequence profiles at 250 million matrix cells per second. Multiprocessor Sun HPC Enterprise serves support computations intermediate in scale between supercomputers and workstations.

The SDSC Advanced Scientific Visualization Laboratory (VisLab) operates a four-processor SGI Onyx Infinite Reality, three SGI Indigo^2 workstations, and a four-processor SGI Challenge L system.

Software

MEME/MAST pattern recognition package. AMBER molecular dynamics package. Profile analysis package. MSMS molecular surface calculation. CMAP/dCMISS continuum mechanics modeling software.

1. Bailey, T. L. and Gribskow, M., Combining evidence using p-values: Application to sequence homology searches. *Bioinformatics,* in press.
2. Grundy, W. N., Bailey, T. L., and Elkan, C. P., ParaMEME: A parallel implementation and a Web interface for a DNA and protein motif discovery tool. *Computer Applications in the Biological Sciences (CABIOS)* 12:303–310, 1997.
3. Bailey, T. L. and Gribskov, M., Score distributions for simultaneous matching to multiple motifs. *Journal of Computational Biology* 4:45–59, 1997.

Parallel Computing Resource for Structural Biology

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Research Emphasis

Methods for simulating structure, function, and dynamics of biological macromolecules. Programs for molecular dynamics simulations with free-energy methods and calculation of long-range electrostatic forces, methods to apply quantum-mechanical methods to large molecules, and an interactive graphics/dynamics interface. Programs for scalable parallel computers. Collaborative effort of biophysicists, physical chemists, computer scientists, mathematicians, and engineers at the University of North Carolina, Duke University, and New York University.

Current Research

Rapid calculation of long-range forces: DPMTA uses multipole/tree code algorithms, with distributed parallelism, extension to periodic systems, calculation of contributions to the pressure and inclusion of both $1/r$ and $1/r^6$ terms, and has been interfaced with the Sigma dynamics code. PME is based on Darden's efficient code that implements the Ewald method.

Interactive graphics/molecular dynamics package for molecular design: The "steered" dynamics tool implements visualization and interactive dynamics simulation. Latest application has been in studies of binding (and unbinding) of small molecules to proteins.

Long time-step dynamics: Significant speed-up of dynamics simulation may be possible via new methods for doing molecular dynamics simulations with long time steps.

Molecular dynamics code (Sigma): Latest release (2.2) includes DPMTA and PME codes, and is compatible with both X-plor and AMBER programs; a parallel version (2.3) is being adapted to the Power Challenge.

Quantum mechanical methods: (Parallel) codes based on density functional theory and semi-empirical methods use the divide-and-conquer method by which the computation scales linearly with the number of atoms for large systems.

Collaborative research projects: Conformational stability of proteins; equilibria and kinetics of protein–small molecule interactions; structure/function of enzymes; protein structure by statistical geometry; distinguishing and correcting misfolded protein models.

Resource Capabilities

Hardware

Cluster of Hewlett Packard 735-125 workstations. Silicon Graphics Power Challenge computer with Onyx graphics, Silicon Graphics Origin 200.

Software

Sigma: Performs molecular dynamics simulations of biological macromolecules. *SMD*: Performs steered dynamics = interactive graphics/dynamics interface for manipulation of molecular structure during continuous molecular dynamics simulation. *Dowser:* Finds internal cavities and assesses their hydrophilicity from the energy for transfer of a water molecule. *FAMBE:* Computers solvation free energy for a continuum dielectric model, using the boundary element method, with adaptive surface grid. *SIMS:* Computes a smooth (singularity-free) molecular surface as a grid that is invariant to molecular rotation or translation (used with FAMBE). *DPMTA:* Parallel code for evaluating pair-wise N-body energies and forces via the fast multipole method. *PME:* Parallel code for evaluating long-range electrostatic forces as the Ewald sum.

1. Nyland, L., Prins, J., Yun, R. H., Hermans, J., Kum, H.-C., Wang, L., Achieving scalable parallel molecular dynamics using dynamic spatial domain decomposition techniques. *Journal of Parallel Distribution Computer IEEE*, in press.
2. Board, J. A., Humphreys, C. W., Lambert, C. G., Rankin, W. T., and Toukmaji, A. Y., Ewald and multipole methods for periodic N-body problems. *1997 Proceedings*, Society of Industrial and Applied Mathematicians.
3. Lee, T.-S., York, D., and Yang, W., Linear-scaling semiempirical quantum calculations for macromolecules. *Journal of Chemical Physics* 105:2744–2750, 1996.

Parallel Processing Resource for Biomedical Scientists

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Research Emphasis

Core research focuses on the advancement of globally scalable, parallel, high-performance computing; the improvement of computational algorithms and methodologies; and their application to molecular structure research, particularly the protein folding problem. The parallel resource emphasizes the integration of computer science research into the computational work of biomedical scientists and is aimed at global optimization, imaging, and structure-based drug design. Collaborative studies include structure prediction of peptides via global optimization; dynamic simulations of acetylcholinesterase; computational structure, function, and selectivity of biological systems; drug design; and new methods for biomolecular structure determination. Parallel resource core research and collaborations are growing a stronger imaging emphasis with work on optimization for image segmentation for lung nodule detection; high-resolution and quantitative ultrasonic imaging; ration design of MRI contrast enhancement agents and other MRI research; and development of improved 3-D visualization techniques for multiphoton microscopy.

Resource Capabilities

160-processor IBM RS/6000 POWER parallel system (SP); suite of computational chemistry software; ECEPP/3 flexible docking program. The Visual Insight Zone offers high-end visualization resources, including a virtual reality CAVE™ supported by a 20-processor SGI Onyx with two Reality Engines.

1. Liwo, A., Oldziej, S., Pincus, M. R., Wawak, R. J., Rackovsky, S., and Scheraga, H. A., A united-residue force field for off-lattice protein-structure simulations. I: Functional forms and parameters of long-range side-chain interaction potentials from protein crystal data. *Journal of Computational Chemistry* 18:874–887, 1997.
2. Li, Y., Piecewise differentiable minimization for ill-posed inverse problems. In *Large Scale Optimization with Applications to Inverse Problems, Optimal Control and Design, and Molecular and Structural Optimization* (Biegler, L. T., Coleman, T. F., Conn, A. R., and Santosa, F. N., eds.). New York: Springer, 1997, pp. 63–79.
3. Gueron, S. and Salloway, D., Spatial interpolation methods for integrating Newton's equation in multiple dimensions. *Journal of Computational Physics* 129:87–100, 1996.
4. Hao, M.-H. and Scheraga, H. A., Optimizing potential functions for protein folding. *Journal of Physical Chemistry* 100:14540–14548, 1996.

Prophet: A National Resource for Life Science Research

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Research Emphasis

Development of the Prophet System. Prophet is a comprehensive software system that gives researchers tools for data analysis and management, graphics, statistics and mathematical modeling, and sequence analysis—all available through a single, point-and-click, graphical user interface. With Prophet you only have to learn one package, but you get four tools.

Current Research

Unlike many commercial packages that focus on generic applications, Prophet has been designed for and with biomedical researchers. Biomedical researchers throughout the world use Prophet to manage and analyze their research data. Scientists at universities, research centers, hospitals, government laboratories, and commercial facilities use Prophet for clinical research, biochemistry, chemistry, immunology, biology, oncology, epidemiology, microbiology, and pharmacology. Prophet also offers a Web-based statistical advisor called StatGuide.

Resource Capabilities

Hardware

Prophet will run on PCs and UNIX workstations, including: PCs running Windows 95 and Windows NT 3.51 or higher; Sun Microsystems SPARC stations running Solaris 2.4 or higher; Silicon Graphics computers including the SGI Indigo series running IRIX version 5.2.

Software

PC requirements: Processor, 486 or better with minimum memory 16 Mbytes. Disk requirements: Distribution is ~18 Mbytes.

Resource Facility for Population Kinetics

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Research Emphasis

The Resource Facility for Population Kinetics (RFPK) promotes application of computer modeling in biomedical research, focusing on compartmental population kinetics. Population kinetics is the methodology used to quantify intersubject variability in kinetic studies. It is widely used in pharmacokinetic studies, since it is the key to the understanding of how drugs behave in humans and animals. In metabolic (e.g., tracer) kinetic studies, it is used to identify those parameters in a model that change when comparing two populations.

RFPK is distributed at the University of Washington and the University of Padua, Italy. Both contribute unique expertise to the project. The administrative core is located at the University of Washington.

Current Research

A growing number of researchers recognize the importance of software tools in this area and the need for individuals with the expertise to develop and apply them. RFPK provides that expertise, together with the development of general purpose algorithms for population kinetics and the theory behind them.

RFPK goals are the development and application of modeling technology to biomedical problems; the development of general purpose algorithms for population kinetics, and making these algorithms easy to use through the development of graphical user interfaces for compartmental models; supporting collaborative projects to help in design and application of the software tools; providing service and training to the user community; and disseminating technology, expertise, and accomplishments.

Resource Capabilities

Software

The proposed software tools for population kinetics will be designed in a modularized fashion. Some modules will be made available to other software developers, thus extending the areas of application of the new computational capabilities. The software tools will be developed and released in stages, so that users can start applying the technology and give feedback for future developments. What will make these tools unique is that there is no one software package that provides both easy model building capability and the standard population kinetic methodologies: Parametric, nonparametric, and two-stage. Thus, the software tools will greatly enhance the overall quality of research in all types of kinetic studies.

Hardware

University of Washington facility: PCs and Macintoshes.
University of Padua facility: UNIX workstations, PCs, and Macintoshes.

Resource for Biomolecular Graphics

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Research Emphasis

The Resource for Biomolecular Graphics creates innovative computational and visualization methods for solving molecular recognition problems in a wide range of applications, including drug design, protein engineering, biomaterials design, and bioremediation. Resource objectives include: Design, implementation, and integration of visualization and computational tools for structural biology; application of these software tools to problems in medicinal chemistry and molecular biology with particular emphasis on elucidation of molecular structure using magnetic resonance spectroscopy (NMR), studies of molecular interactions, drug design, and protein engineering; and dissemination, as documented source code, of the software developed at this resource to allow others to use the software both for their own research applications and as a starting point and training tool for specialized applications.

Current Research

Design and development of new software methods, including Chimera, an extensible interactive molecular graphics system; studies focused on protein-ligand and protein-protein interactions; "re-engineering" of native proteins in order to promote novel biochemical functions; and studies of structural proteins such as collagen. The research program is dynamic and details are continually changing as new discoveries are made. For the most up-to-date information, consult the resource Web page at the URL above.

Resource Capabilities

Hardware

Hardware includes a high-performance, departmental-class server used for storage and searches of sequence and structure databases and for performing theoretical studies on protein and nucleic acid structure and function. High-performance workstations from Silicon Graphics, Digital Equipment, and Hewlett Packard are used for generating three-dimensional interactive molecular models. All systems are interconnected via a high-speed network and capable of distributed computations. Color hard copy (slides, transparencies, and prints) and high-quality video are used for disseminating results.

Software

A variety of software packages are available. The primary molecular visualization application in use is MidasPlus, an advanced molecular modeling system developed at the Resource and used to display and interactively manipulate macromolecules such as proteins and nucleic acids. Other locally developed applications include MARDIGRAS, a program for calculating proton-proton distances from cross-peak intensities measured from two-dimensional NMR experiments; CORMA, a program for calculating the dipole-dipole relaxation matrix for a system of protons and converting that to intensities expected for a two-dimensional NMR experiment; and SPARKY, an interactive user-friendly software tool for performing NMR cross-peak assignments. See the resource Web site for additional details.

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2. Huang, C. C., Couch, G. S., Pettersen, E. F., and Ferrin, T. E., Chimera: Extensible molecular modeling application constructed using standard components. In *Pacific Symposium on Biocomputing '96* (Hunter, L. and Klein, T. E., eds.). Singapore: World Scientific Publishing, 1996, p. 724.
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Resource for Macromolecular Modeling and Bioinformatics

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Research Emphasis

Studying the structure and function of biopolymers and biopolymer aggregates by theoretical and computational means; investigating genomes from different origins (from viruses to mammals) and analyzing their organization and expression scheme to fully functional biopolymers; molecular dynamics simulations of biological macromolecules (proteins, DNA, lipids, and others) and supramolecular structures, in particular very large systems; interactive modeling and visualization of remote simulations; distributing MDScope, an in-house–developed molecular modeling program.

Current Research

Steered molecular dynamics and bioinformatics projects; efficient, distributed molecular dynamics programs on workstation clusters and massively parallel machines; interactive molecular modeling with user interface on standard graphics workstations or 3-D projection systems; interactive molecular dynamics using a molecular dynamics program executed on remote high-performance machines; efficient evaluation of force fields and efficient integration schemes for simulation of very large biomolecular systems.

Resource Capabilities

Instruments

An 8-way symmetric multiprocessor SGI Onyx2 Infinite Reality Rack equipped with eight 195 Mhz R10000 processors sharing one gigabyte (GB) of RAM and 16 GB in disk space. The Onyx2 is integrated into our current asynchronous transfer mode (ATM) system, and it drives our 3-D visualization facility. The computer hardware also includes 14 HP 735/125 workstations and 4 HP K-series four-way–multiprocessor servers with an aggregate of over 3 GB of RAM and 30 GB of disk space, interconnected with two ATM switches using 100 Mbit/s and 155 Mbit/s fiber optic media; a HP J210, a HP 755/99, and a HP 9000-800 E35 server provide access to 100 GB of disk space to serve the network-wide home and projects directories. Also available is a magneto-optical jukebox with 20 GB of online removable storage space, and a 3-D projection facility with Electrohome 8501LC P43 stereo projector. An SGI Onyx VTX, four SGI Indigo^2 Maximum Impact workstations, a Crimson and two 02 workstations for graphics.

Special Features

MDScope is an integrated set of computational tools that functions as an interactive visual computing environment for the simulation and study of biopolymers. The package serves to visualize biomolecular assemblies, to submit and monitor simulations, and to perform interactive molecular dynamics. At the core of MDScope are three major software components: VMD, a visualization program for interactive display and animation of molecules; NAMD, a parallel message-driven molecular dynamics program; MDComm, a protocol and library for communication between VMD and NAMD. This molecular dynamics package is written in C++, and compatible with SGI and HP machines, as well as with National Supercomputer Center massively parallel computers, running as a parallel or serial program.

1. Balaeff, A., Churchill, M., and Schulten, K., Structure prediction of a complex between the chromosomal protein HMG-D and DNA. *Proteins: Structure, Function, and Genetics* 30:113–135, 1998.
2. Humphrey, W., Dalke, A., and Schulten, K., VMD–Visual molecular dynamics. *Journal of Molecular Graphics* 14:33–38, 1996.
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Resource for the Study of Neural Models of Behavior

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Research Emphasis

Developing state-of-the-art instrumentation and techniques for the monitoring and simulation of behavior in conjunction with relevant neural parameters. To greatly extend the capability to monitor behavior in natural situations, four different technical innovations are being integrated: Equipment to measure eye movements in freely moving head situations; devices for measuring kinematic state, such as arm and hand movements; devices for producing whole-body accelerations; and anthropomorphic devices to simulate experiments and develop experimental protocols. This virtual environment capability supports interdisciplinary experiments in the behavioral, computational, and neuroscience areas.

Current Research

The central feature of human behavior is the information used to direct ongoing cognitive activity. This is known as working memory. Since 1956 it has been known that working memory has a capacity limit of about seven items, but the significance of this small number has not been understood until recently. Studying the transit of information to and from spatial working memory using our special instrumentation reveals the trade-offs that keep working memory small. In addition, our unique instrumentation allows experiments that relate working memory to the body's sensory-motor state.

Resource Capabilities

Innovative instrumentation has been specifically built to study the brain's behaviors at subsecond timescales. The main components are distributed in three laboratories: 1) A virtual reality laboratory allows the simultaneous recording of unrestricted head, eye, and hand movements while human subjects are engaged in visually guided tasks using both real and virtual displays. Two virtual environments have been created. One allows driving in a virtual car. The other allows graphic manipulation using a virtual force generator. 2) A visual and vestibular stimulation facility for human subjects uses virtual displays coupled with a sled rotator device capable of delivering precise angular and linear accelerations in any combination; an animal research laboratory for use with awake behaving monkeys has similar capabilities. 3) An anthropomorphic simulation laboratory uses robotic hardware to simulate sensorimotor coordination. This facility couples an existing high-speed binocular camera control system with an anthropomorphic four-fingered hand.

1. Ballard, D. H., Hayhoe, M. M., Pook, P. K., and Rao, R. P. N., Deictic codes for the embodiment of cognition. *Behavioral & Brain Sciences*, in press.
2. Ballard, D. H., Hayhoe, M. M., and Pelz, J. B., Memory representations in natural tasks. *Journal of Cognitive Neuroscience* 7:1:66–80, 1995.
3. Rao, R. P. N. and Ballard, D. H., An active vision architecture based on iconic representations. *AI Journal* 78:461–505, 1995.
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Supercomputing Resources for the Biomedical Community

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Research Emphasis

Biomedical computer programs for and access to high-performance parallel and vector computing resources; computational chemistry, structural biology, computational genetics, computational neural science, image reconstruction, and scientific visualization. Core and collaborative research, an educational program, and support for users.

Current Research

Sequence analysis, structural biology and computational chemistry, proteomics and bioinformatics. Development of sequence alignment algorithms that use structural, chemical, or biochemical information in addition to the sequence; algorithms for the analysis of multiple sequence alignment data; classification and analysis of gene and protein superfamilies; a protein structure database that relates the sequence to secondary, supersecondary, and tertiary structure information; models for understanding divalent metal ion binding sites in proteins and nucleic acids; algorithms to describe the long-range interactions in molecular mechanics computations.

Resource Capabilities

Hardware

The Cray T3E massively parallel processor has 512 DEC Alpha application processing elements (half running at 300 MHz and half at 450 MHz) and 23 command processing elements (PEs), with a total of 64 gigabytes of memory and a peak performance of 384 billion floating point operations per second. The CRAY Y-MP/C90, a 16-processor, 512 million word parallel vector supercomputer with a 512 million word Solid State Storage device, has a peak computational rate of close to 16 billion floating point calculations per second; 192 gigabytes of primary disk space.

Two Cray Research J916 8-1024 systems: 8-processor, 1024-megabytes parallel vector systems with approximately 70 gigabytes of disk storage. A prototypical workstation cluster for experimentation in loosely coupled parallel application development of 12 DEC Alpha workstations interconnected by an FDDI DEC Gigaswitch with two DEC Alpha workstations serving as front ends. The front-end environment includes a VMS cluster (two DEC VAX CPUs, two DEC Alpha CPUs, and over 70 gigabytes of disk storage) and two DECstation 5000 servers running UNIX.

Software

Over 350 packages in quantum chemistry, molecular modeling, genetic sequencing. All major sequence and structural databases. Most commercial packages for fluid dynamics, structural analysis, finite element analysis, mathematics libraries, equation solvers, tools, and graphics.

Training Facility

25 Silicon Graphics Indy graphics workstations for teaching all workshops, including graphically intensive subjects (e.g., 3-D biomedical applications, molecular modeling) and applications (distributed ray tracing).

1. Deerfield, D. W., II, Holland-Minkley, A. M., Geigel, J., and Nicholas, H. B., Jr., Classification of the environment of protein residues. *Journal of Protein Chemistry* 16:441–447, 1997.
2. Cheatham, T. E., III, Crowley, M. F., Fox, T., and Kollman, P. A., A molecular level picture of the stabilization of A-DNA in mixed ethanol-water solutions. *Proceedings of the National Academy of Sciences* 94:9626–9630, 1997.
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5. Cho, B., Taylor, D. C., Nicholas, H. B., Jr., and Schmidt, F. J., Interacting RNA species identified by combinatorial selection. *Bioorganic & Medicinal Chemistry* 5:1107–1113, 1997.

Theoretical Simulation of Biological Systems

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Research Emphasis

New algorithms, models, and software for simulation of biomolecular systems. New methods are developed and implemented in user-friendly software that is distributed via both academic and commercial channels. The software is developed for both serial and parallel machines; a significant component of the research effort is obtaining efficient parallel performance on currently available hardware. Research efforts range from ab initio quantum chemistry to atomic level molecular modeling to reduced models for protein folding.

Current Research

Research in algorithm development includes various models for a continuum treatment of molecular solvation (both classical and quantum chemical self-consistent reaction field), methods for accelerating simulation codes (multiple timescales, fast multipoles, mixed Monte Carlo/molecular dynamics methods), and novel methods for correlated quantum chemical calculations. Effort is also being devoted to the development of new force fields based on polarizable models (e.g., fluctuating charge and polarizable dipole models). Studies of protein folding using simplified protein models and a variety of novel algorithms are being carried out.

Resource Capabilities

Hardware

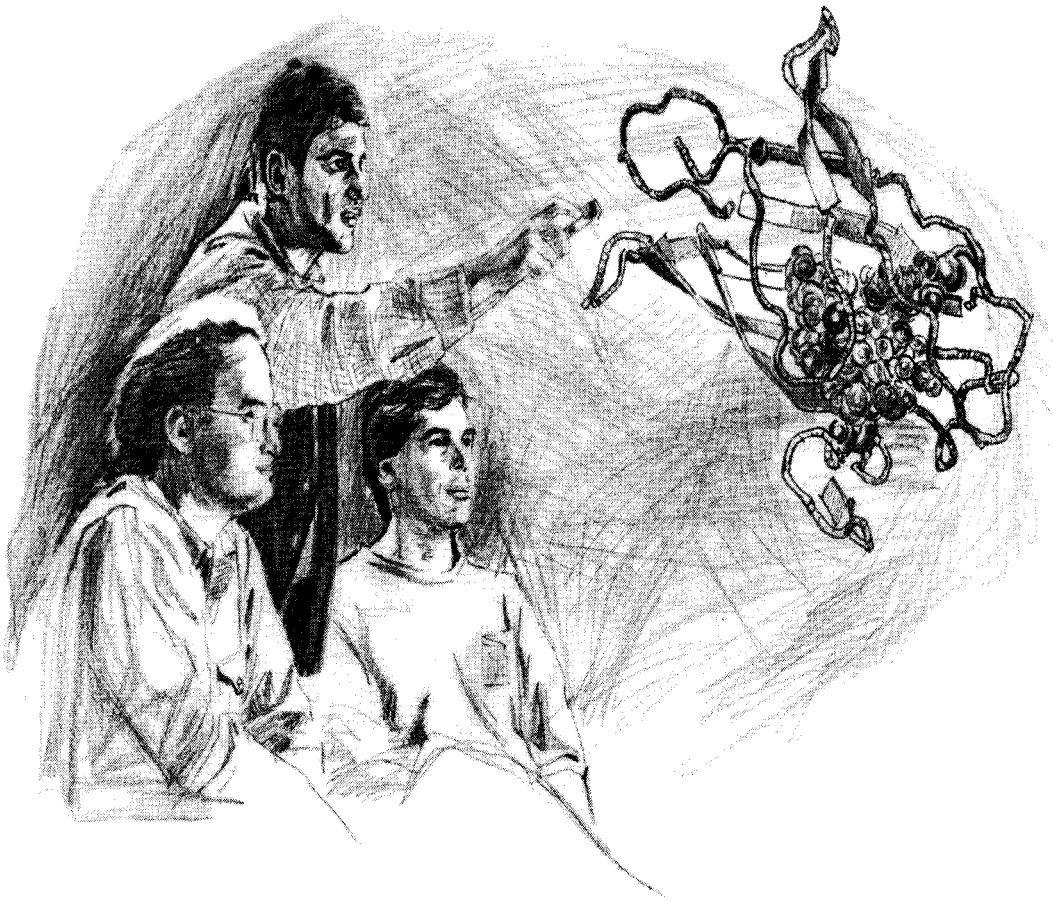
Network equipment: All the newer systems are connected via 100 MHz fast Ethernet. This network is segmented by an 8-port Nbase fast Ethernet switch. The switch has ATM uplink capabilities that permit using a T3 link to the IBM SP2 that is not located at this site. The resource also has a 10 MHz Ethernet LAN segmented by an 8-port ChipCom Ethernet bridge. Users can connect remotely via a Cisco terminal server that has 628.8 Kbps Motorola modems. Computational platforms: 30-node SP2 massively parallel supercomputer (shared with Lamont-Doherty Observatory); 13 Motorola Power PC personal computers; 45 dual processor Pentium Pro 200 PCs.

Software

User-friendly software packages are distributed through commercial and academic channels and are also available for use at the Cornell Theory Center. Currently available packages include DelPhi (continuum electrostatics), Macromodel (molecular modeling), PSGVB (ab initio electronic structure theory), and IMPACT (molecular modeling).

1. Beachy, M., Chasman, D., Murphy, R., Halgren, T., and Friesner, R., Accurate ab initio quantum chemical determination of the relative energetics of peptide conformations and assessment of empirical force fields. *Journal of the American Chemical Society* 119:5908–5920, 1997.
2. Edinger, S., Cortis, C., Shenkin, P. S., and Friesner, R. A., Solvation free energies of peptides: Comparison of approximate continuum solvation models with accurate solution of the Poisson-Boltzmann equation. *Journal of Physical Chemistry* 101:1190–1197, 1997.
3. Gunn, J. and Friesner, R., Computational studies of protein folding. *Annual Review of Biophysics and Biomolecular Structure* 25:315, 1996.
4. Marten, B., Kim, K., Cortis, C., Friesner, R. A., Murphy, R. B., Ringnalda, M. N., Sitkoff, D., and Honig, B., New model for calculation of solvation-free energies: Correction of self-consistent reaction field continuum dielectric theory for short range hydrogen bonding effects. *Journal of Physical Chemistry* 100:11775, 1996.

Synchrotron Radiation



BioCARS Synchrotron Structural Biology Resource

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Research Emphasis

In 1998, when the resource is completed at the Argonne National Laboratory's Advanced Photon Source, it will offer x-ray beams of unusually high brilliance. Experimenters will be able to collect highly accurate x-ray diffraction data in a number of areas: Crystals with very large unit cells; microcrystals; time-resolved diffraction on time scales ranging from seconds to 100 picoseconds; and multiple wavelength anomalous dispersion (MAD) phasing.

Current Research

Design and construction of novel optical elements to deliver the brilliant x-ray beam to the crystals; design and construction of all components necessary to equip one sector at the Advanced Photon Source consisting of one insertion device and one bending magnet beamline; novel forms of x-ray detectors; and strategies for the effective acquisition of precise MAD data, and of time-resolved data.

Resource Capabilities

Instruments

Appropriate hardware and software for experiments in the areas outlined.

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Research Emphasis

To construct and operate facilities at Argonne National Laboratory's Advanced Photon Source (APS) (http://www.aps.anl.gov/) as a national research resource for the study of the structure of partially ordered biological molecules, complexes of biomolecules, cellular structures under conditions similar to those present in living cells, and tissues. The goal of such research is to determine the detailed structure and mechanism of action of biological systems at the molecular level. The techniques employed are x-ray fiber diffraction, x-ray solution scattering, and x-ray absorption spectroscopy, with an emphasis on time-resolved and space-resolved studies, and development of novel techniques. First light was obtained within 2 years: September 1997.

Current Research

Typical applications: X-ray diffraction of muscle fibers, Langmuir Blodgett films, and membrane/protein systems, solution scattering, protein folding. XAFS studies of metalloproteins and complexes. Instrumentation development. Novel detector designs. Improved data acquisition, data evaluation, and robust data analysis methods.

Facilities

APS undulator A beamline, fixed exit height, cryogenically cooled silicon monochromator, energy range 4–40 KeV, harmonic rejection/focusing mirror, crystal sagittal focusing. Rapid scanning capability. LN2 cooled Silicon (111) and Si(331) monochromators. Measured flux at 12 KeV is ~2 x 10^{13} photons/sec into focal spot that is independently vertically adjustable between < 40 µm to ~1 mm vertical, and horizontally adjustable from < 100 µm to ~4 mm. 7 m long optical table. Ionization chambers, large acceptance multilayer analyzer/detector for fluorescence XAFS and microprobe; CCD, image plate, and high rate linear multielement detector for SAS. Software for time-resolved data acquisition; shortest time slicing interval in standard setup for XAFS and MED ~ 10 µs. Apparatus for optical monitoring of sample integrity; polarized XAFS goniometer; stopped flow system; low vibration closed cycle helium refrigerator for sample cooling. Sample preparation and characterization laboratory adjacent to beamline; electronics laboratory; SGI 02 workstation with data analysis software for XAFS and SAS. Periodic training workshops.

Macromolecular Diffraction Biotechnology Resource

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Research Emphasis

The Cornell High Energy Synchrotron Source (CHESS) is a general purpose laboratory for synchrotron radiation studies. Three CHESS stations, widely used for macromolecular crystallography, are supported by the MacCHESS Research Resource. Station A-1 receives radiation from a 24-pole wiggler and provides a doubly focused x-ray beam at the sample. The station normally operates at a wavelength of 0.91 Å. Station F-1 is nearly identical to station A-1 but is part of a BL-2 level biological containment facility. Stations A-1 and F-1 are primarily used for monochromatic oscillation data collection. Station F-2 is a doubly focused wiggler station with a double crystal monochromator. The energy can be rapidly tuned over the 4–40 KeV range and is ideally suited for MAD phasing experiments. MacCHESS provides both image plate and CCD-based x-ray detectors and apparatus for crystal freezing. Special emphasis is placed on crystals with very large unit cells, microdiffraction, ultrahigh-resolution data collection, and anomalous scattering.

Resource Capabilities

Efforts are directed toward the development of novel x-ray optics, diffraction techniques, and x-ray detectors. Optics under investigation include focusing mirrors, transmission mirrors, and layered synthetic microstructures suitable for both monochromatic and polychromatic diffraction. Most outside users have employed focusing, nontunable radiation and an oscillation camera. Unit cell dimensions up to 1,000 Å have been readily resolved. Typical exposure time per oscillation photograph is 30 seconds. User research is often directed toward determination of virus structures and complexes of viruses with antiviral drugs and antiviral antibodies.

Instruments

Monochromators on the three diffraction beam lines deliver doubly focused, tunable wiggler radiation in the range from 0.7 to 2.0 Å, or nonfocused, tunable-dipole radiation down to 0.3 Å. Diffraction apparatus includes oscillation cameras, image plate scanners, and CCD-based x-ray detectors. Two crystal coolers that cover the range from –50° to +70° C and –180° to –50° C are available.

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2. Xu, W., Harrison, S. C., and Eck, M. J., Three-dimensional structure of human c-Src. *Nature* 385:595–602, 1997.
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4. Cate, J. H., Gooding, A. R., Podell, E., Zhou, K., Golden, B. L., Kundrot, C. E., Cech, T. R., and Doudna, J. A., Crystal structure of a group I ribozyme domain: Principles of RNA packing. *Science* 273:1678–1685, 1996.

Regional Center for Time-Resolved Synchrotron Spectroscopy

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Research Emphasis

The Regional Center for Time-Resolved Synchrotron Spectroscopy at Albert Einstein College of Medicine and the National Synchrotron Light Source focuses on technology development in the general area of structural kinetics of macromolecules. Synchrotron x-ray and infrared beams, with unique flux and brightness properties, are used in three major areas of research: Time-resolved x-ray footprinting studies examine the conformational dynamics of DNA, RNA, and proteins during ligand binding, folding, and catalysis; time-resolved far- and mid-infrared studies examine the dynamics and folding of proteins on microsecond to millisecond timescales; time-resolved x-ray spectroscopy is used to examine the structure of metal centers in metalloproteins, specifically to isolate the structures of intermediate states.

Current Research

Structure of metalloprotein active sites, time-resolved metalloprotein structures, development of improved data acquisition and analysis techniques in the area of x-ray absorption fine structure. Structure of membranes and muscle fibers. Folding and dynamics of ribozymes, DNA-protein interactions, protein folding. Dynamics of retinal proteins. Development of millisecond hydroxyl-radical footprinting techniques coupled to stopped-flow devices. Development of time-resolved mid- and far-infrared spectroscopy techniques.

Resource Capabilities

Instruments at the National Synchrotron Light Source: Synchrotron x-ray beamlines for spectroscopy, diffraction, and x-ray footprinting. Synchrotron infrared beamline. Double crystal focusing monochromator, focusing mirror. Huber diffractometer, Canberra 13-element Germanium detector, Continuum Nd: YAG nanosecond laser with doubling crystals, Displex (helium) cryostat, stopped-flow for x-ray footprinting using white radiation. Biochemistry laboratory and cold room.

Instruments at the Albert Einstein College of Medicine: Laser and infrared spectroscopy laboratory, biochemistry laboratory.

1. Wang, H., Peng, G., Miller, L. M., Scheuring, E. M., George, S. J., Chance, M. R., and Cramer, S. P., Iron L-edge X-ray absorption spectroscopy of myoglobin complexes and photolysis products. *Journal of the American Chemical Society* 119:4921–4928, 1997.
2. Sclavi, B., Woodson, S., Sullivan, M., Chance, M. R., and Brenowitz, M., Time-resolved synchrotron X-ray "footprinting," a new approach to the study of nucleic acid structure and function: Application to protein-DNA interactions and RNA folding. *Journal of Molecular Biology* 266:144–159, 1997.
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Synchrotron Radiation Biotechnology Resource

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Research Emphasis

Stanford Synchrotron Radiation Laboratory (SSRL) provides synchrotron radiation for research in fields including structural molecular biology. Synchrotron radiation is available on a peer-reviewed proposal basis on 26 experimental stations. This program explicitly provides R&D and user support for structural molecular biology research in protein crystallography (PX), x-ray absorption spectroscopy (XAS), and small-angle x-ray scattering (SAXS).

State-of-the-art PX data collection/data reduction stations are available at SSRL for high-speed data collection, MAD phasing studies, and high-resolution crystallography. Data are typically collected at cryogenic temperatures. XAS capabilities include high-resolution multielement detectors and low-temperature cryostats on stations covering the energy range 2–30 KeV. For SAXS studies there is instrumentation for both static and rapid mixing time-resolved studies. A new low-angle single crystal diffraction system is available.

Current Research

Protein crystallography: Two rapid turnaround data collection stations, equipped with automated MAR-Research imaging-plate x-ray detectors are available on wiggler beam lines (7-1 and 9-1). BL7-1 is run at a fixed x-ray wavelength of 1.08 Å with a MAR-300 detector, and BL9-1 is a fixed wavelength station for x-ray wavelengths that can be set within the range ~1.05 Å to ~0.75 Å (normally set to 0.9798 Å). BL9-1 is also used for very-high–resolution studies (<0.9 Å). Multiwavelength data are collected, for MAD-phasing experiments, on the tunable (~0.85–2.0 Å) bending magnet station BL1-5, equipped with Fuji imaging plates (scanned off-line). A new wiggler station (BL9-2) for MAD and high-resolution experiments is currently being completed, and will be equipped with an ADSC Quantum-4 matrix CCD detector. Each of the PX stations is equipped with a LN_2 cryostat and fast DEC Alpha and SGI computer systems for data reduction and graphics. Equipment for pressurization with Xe gas and flash-cooling of crystals is available at the stations.

Small-angle x-ray scattering: A multipurpose SAXS camera is available for use on a semi-dedicated wiggler station (up to 45% of total beam time). The camera utilizes either a one-dimensional position-sensitive wire detector, a quadrant detector, or an imaging plate detector. A low-noise 6" diameter CCD detector will be added in 1998. A stopped-flow rapid mixer is available for time-resolved SAXS studies of proteins in solution. A low-angle single crystal diffraction system (10–700 Å) is available. Data collection and analysis is performed on DEC Alpha, VAX, and PC computer systems.

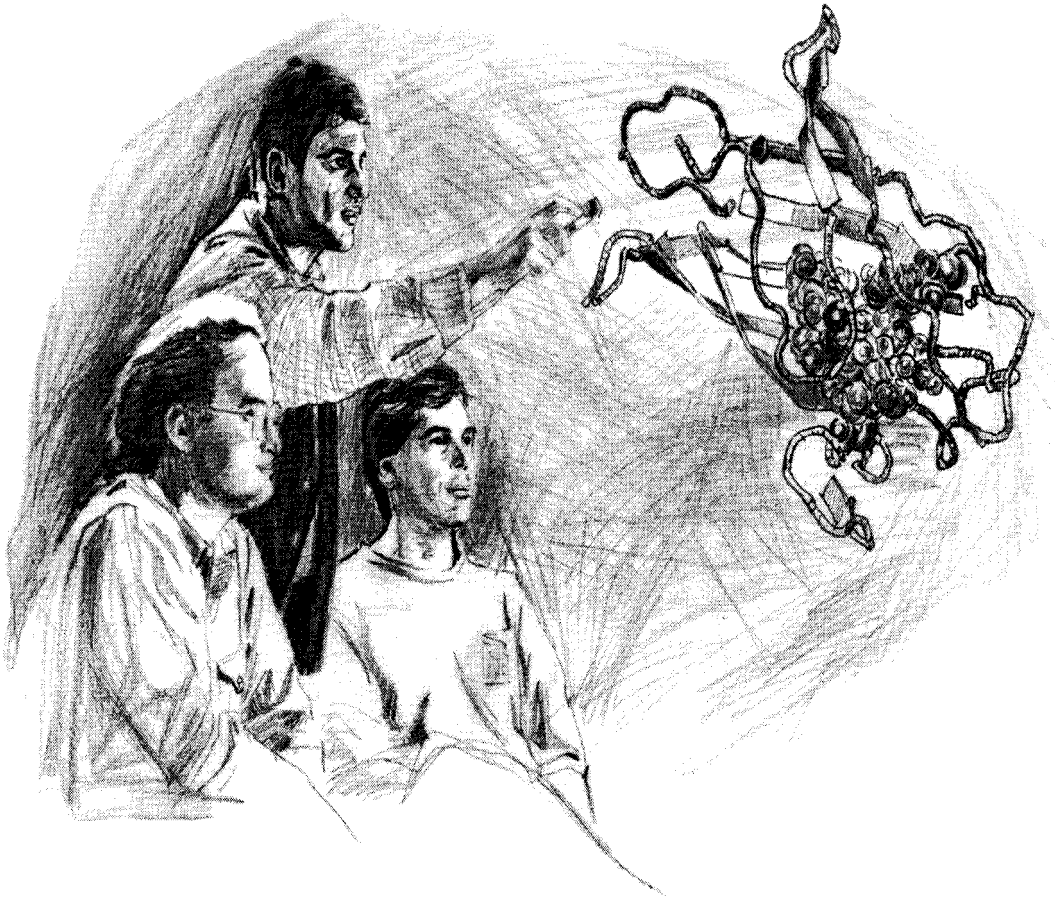
X-ray absorption spectroscopy: One dedicated wiggler and six shared wiggler or bending magnet stations are available, equipped with high throughput/high energy resolution 13-element Ge array or ionization chamber detectors for fluorescence measurements of biological samples in the millimolar concentration range. A dedicated high-intensity wiggler station is being commissioned that will be equipped with a 30-element Ge array detector. Four liquid He cryostats are available for data collection at temperatures as low as 4 K. Interactive software on DEC Alpha stations allow users to measure and analyze XAS data and display results online.

Resource Capabilities

Additional Facilities

A central computational facility. High-performance DEC Alpha and SGI workstations. A lab-wide high-speed network and fast external network access for data transfer to user home institutions. Two supporting biochemical/chemical laboratories including coldrooms, instrumentation, and laboratory equipment/supplies.

Other Biomedical Technology Activities



Biomedical Technology Resource Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6160
Bethesda, MD 20892-7965
301-435-0755 Fax: 301-480-3775
E-mail: btadir@ncrr.nih.gov

Purpose

Biomedical Technology Resource Grants (P41) support research and development of new technologies or instruments with broad biomedical application using the latest advances in engineering, the physical sciences, mathematics, and computer science. Currently, NCRR funds research and development activities at more than 60 biomedical technology resource centers at locations across the country, primarily at major academic institutions. Principal investigators at the centers lead scientific teams to discover, create, develop, and disseminate technological innovations that have broad applications to studies of biology, medicine, behavior, and health. Each center functions as both a technological resource and an intellectual resource, with an infrastructure that permits staff scientists to react rapidly and effectively to emerging biomedical research needs. The multidisciplinary environment of each center stimulates innovation and collaboration among physical scientists, engineers, and biomedical scientists. The centers also must make their technologies available to a user community of biomedical researchers.

In addition to their role in advancing biomedical science, these centers provide a cost-effective mechanism for sharing of very complex and costly technological resources and an efficient way for leveraging federal funds in an era of constrained resources. Each year, nearly 6,000 biomedical investigators from across the country are either collaborators or users of cutting-edge technologies offered by this national network of biomedical technology resource centers supported by NCRR. In addition to these users, even more investigators have benefited from center-sponsored workshops, consultations, and other training activities.

Application

Resource grant applications should be submitted on Form PHS 398, Application for Research Grant. Applicants must contact program staff before submitting an application for a resource center.

Review Criteria

Applicant institutions are evaluated according to the following five main criteria: Technological research and development, collaborative research, service, training, and dissemination.

Funding

The award of grants is contingent on the receipt of applications of high scientific merit, relevance to the mission of the Biomedical Technology area of the NCRR, and availability of appropriated funds.

Investigator-Initiated Biomedical Technology Research Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6160
Bethesda, MD 20892-7965
301-435-0755 Fax: 301-480-3775
E-mail: btadir@ncrr.nih.gov

Purpose

Investigator-initiated Biomedical Technology Research Grants (R01) support research and development to improve existing instruments or to develop new instruments or technologies that may have broad application to biomedical research. The research supported may involve conceptualization, design, fabrication, and/or testing of the technology with the overall objective leading to a new or more powerful technology for biomedical research.

Application

R01 applications should be submitted on Form PHS 398, Application for Research Grant, and must be prepared according to NIH guidelines for this award. A well-defined research agenda that addresses a specific instrument or technology should be included. Application deadlines are February 1, June 1, and October 1.

Review Criteria

Applications will be evaluated on scientific, technical, or biomedical significance and originality of the proposed research; adequacy of proposed engineering approaches and methods; qualifications of the principal investigator; availability of resources needed; reasonableness of the budget; and adequacy of protective measures against adverse effects on humans, animals, or the environment.

Funding

The award of grants is contingent on the receipt of applications of high scientific merit, relevance to the mission of the Biomedical Technology area of the NCRR, and availability of appropriated funds. If the requested direct cost in any one year exceeds $500,000, applicants must contact an NCRR Biomedical Technology program official prior to submitting an application.

Exploratory/ Developmental Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6160
Bethesda, MD 20892-7965
301-435-0755 Fax: 301-480-3775
E-mail: btadir@ncrr.nih.gov

Purpose

This funding mechanism (R21) was initiated in l997 by the Biomedical Technology area to stimulate exploration of new technologies and new approaches, or to challenge existing paradigms in technologies related to biomedical research. Proposals are expected to encompass work at the edge of new frontiers or the limits of understanding of a biomedical research problem. This grant support offers researchers an opportunity to collect preliminary data to support future applications for funding by NCRR or other NIH components.

The projects should provide the opportunity to develop new technologies, methods, devices, and materials that provide greater understanding of fundamental elements of biological phenomena. These efforts should lead to new approaches to the solution of basic research questions in order to prevent, diagnose, and treat disease and disability and ultimately to improve human health.

Application

The technologies/instruments/methodologies to be developed under this program must be applicable to a variety of NIH research areas. Applications to develop technologies that apply only to one categorical NIH institute or a specific disease generally do not meet the guidelines for this program. Such applications will be considered only if the applicant clearly demonstrates the long-term potential of the technology for having a broad impact on biomedical research.

Applications are to be submitted on the grant application Form PHS 398. Application deadlines are June 1 and September 1.

Review Criteria

Evaluations of proposed research will address the degree of innovation, presence of risk, and the potential for affecting biomedical research.

Funding

The award of grants is contingent on the receipt of applications of high scientific merit; relevance to the mission of the Biomedical Technology area of the NCRR; and availability of appropriated funds. Funding is limited to $75,000 in direct costs per year for up to two years. Grants are not renewable.

Shared Instrumentation Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6154
Bethesda, MD 20892-7965
301-435-0772 Fax: 301-480-3659
E-mail: SIG@ncrr.nih.gov

Purpose

The objective of the Shared Instrumentation Grants (SIG) program (S10) is to make available to institutions expensive research instruments that can only be justified on a shared-use basis and for which meritorious research projects are described. The SIG program provides a cost-effective mechanism for groups of NIH-supported investigators to obtain commercially available, technologically sophisticated equipment costing more than $100,000.

Examples of key instruments needed to understand fundamental biological processes include, but are not limited to: High-resolution mass spectrometers and high throughput protein and nucleic acid sequencers used for the mapping, sequencing, and analysis of DNA and proteins; high-field NMR spectrometers, x-ray sources, and detectors to probe the 3-D structure of proteins; confocal microscopes, NMR imaging devices, cell sorters, and biosensors to study functional imaging of living systems; high-performance computers to gather, process, archive, and retrieve complex information sets.

Application

SIG applications are submitted on Form PHS 398, Application for Research Grant. Applications may be submitted for instruments costing at least $100,000. There is no upper limit on the cost of the instrument, but the maximum award is $400,000. The once-a-year deadline is in March.

To obtain an instrument that costs over $500,000, applicants may be eligible for joint funding by NIH and the National Science Foundation and should inquire for more information.

Review Criteria

Instrument-specific study sections review SIG applications and base their evaluations on the following criteria: Demonstrated need for a new or updated instrument for a major user group of three or more investigators; enhancement of the NIH-funded research projects; appropriate technical expertise; adequacy of the plan to administer the grant and assure equitable use; institutional commitment; and benefit to the biomedical research community.

Funding

Awards are made to institutions only, are for one year, and are not renewable. The institution must meet those costs required to place the instrument in operational order as well the maintenance, support personnel, and service costs associated with its use.

Small Business Innovation Research Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6160
Bethesda, MD 20892-7965
301-435-0755 Fax: 301-480-3775
E-mail: btadir@ncrr.nih.gov

Purpose

The Small Business Innovation Research (SBIR) Grants (R43) program is a set-aside program designed to support innovative research conducted by small business concerns that has the potential for commercialization of the subject of research.

For instrumentation and specialized technologies research and development in biomedical research, small businesses may be interested in, but are not limited to: New or improved instruments, devices, and related methodologies to facilitate biomedical or behavioral research (e.g., mass spectrometry, nuclear magnetic resonance, electron spin resonance, x-ray absorption/diffraction, flow cytometry); applications of computer science/technology to biomedical or behavioral research problems (e.g., computer visualization, image processing, computer modeling/simulation including neural networks, structure-based drug design); biomedical engineering approaches for basic/clinical research with potential for preventing or treating disease and/or significantly reducing health care costs (e.g., biomaterials, microsensors, monitoring devices, non-invasive diagnostic approaches, alternatives to radioactive-based methods, robotics, and drug delivery systems).

Application

The application receipt dates for SBIR grant applications are April 15, August 15, and December 15. Program solicitations and other details are available at the NIH Web site, http://www.nih.gov/grants/funding/sbir.htm.

Review Criteria

The following criteria will be used in considering the scientific and technical merit of each application: Soundness and technical merit of the proposed approach; qualifications of the proposed principal investigator, supporting staff, and consultants; the scientific, technical, or technological innovation of the proposed research; potential of the proposed research for commercial application; appropriateness of the budget requested; adequacy and suitability of the facilities and research environment; and, where applicable, the adequacy of assurances detailing the proposed means for (a) safeguarding human or animal subjects, and/or (b) protecting against or minimizing any adverse effect on the environment.

Funding

SBIR grant awards are $100,000 for a period of up to 6 months for pilot studies of new biomedical technologies and improvements in existing ones (Phase I). A follow-up grant of $750,000 for a period of up to 2 years may be awarded after competitive review if the Phase I project meets its goals and is found to have technical and scientific merit as well as commercial potential (Phase II).

Small Business Technology Transfer Grants

For more information, contact
Biomedical Technology Area
National Center for Research Resources
6705 Rockledge Drive, Rm. 6160
Bethesda, MD 20892-7965
301-435-0755 Fax: 301-480-3775
E-mail: btadir@ncrr.nih.gov

Purpose

The Small Business Technology Transfer (STTR) Grants (R41) program is designed to support innovative research that has the potential for commercialization of the subject of the research, conducted cooperatively by a small business concern and a research institution. At least 40 percent of the research project is to be conducted by the small business concern and at least 30 percent of the work is to be conducted by the single, "partnering" research institution.

For instrumentation and specialized technologies research and development in biomedical research, small businesses may be interested in, but are not limited to: New or improved instruments, devices, and related methodologies to facilitate biomedical or behavioral research (e.g., mass spectrometry, nuclear magnetic resonance, electron spin resonance, x-ray absorption/diffraction, flow cytometry); applications of computer science/technology to biomedical or behavioral research problems (e.g., computer visualization, image processing, computer modeling/simulation including neural networks, structure-based drug design); biomedical engineering approaches for basic/clinical research that have potential for preventing or treating disease and/or significantly reducing health care costs (e.g., biomaterials, microsensors, monitoring devices, noninvasive diagnostic approaches, alternatives to radioactive-based methods, robotics, and drug delivery systems).

Application

The application receipt dates for STTR grants are April 1, August 1, and December 1. Program solicitations and other details are available at the NIH Web site, http://www.nih.gov/grants/funding/sbir.htm.

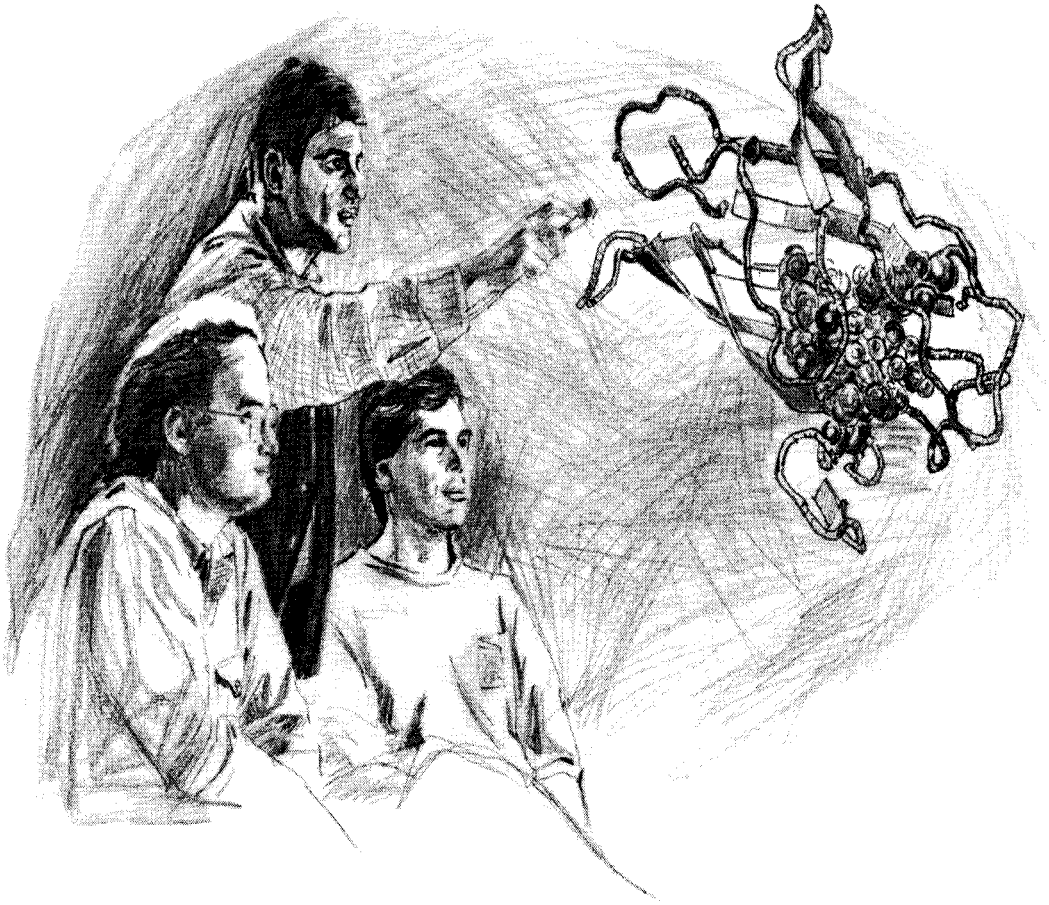
Review Criteria

In considering the scientific and technical merit of each application, the following criteria will be used: Soundness and technical merit of the proposed approach; qualifications of the proposed principal investigator, supporting staff, and consultants; scientific, technical, or technological innovation of the proposed research; potential of the proposed research for commercial application; appropriateness of the budget requested; adequacy and suitability of the facilities and research environment; and, where applicable, the adequacy of assurances detailing the proposed means for (a) safeguarding human or animal subjects, and/or (b) protecting against or minimizing any adverse effect on the environment.

Funding

STTR grant awards are $100,000 for up to one year for Phase I to determine the project's scientific and technical merit and feasibility, and $500,000 for up to two years for Phase II to continue Phase I research.

Indexes



Name Index

Geographic Index

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